



VOLUME 25

*Chicago Number*

NUMBER 1

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THE  
MEDICAL CLINICS  
OF  
NORTH AMERICA

*JANUARY, 1941*

PHILADELPHIA AND LONDON

W. B. SAUNDERS COMPANY

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SQUARE, PHILADELPHIA.

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January, 1941

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**SYMPOSIUM ON PAIN**

PAIN is a danger signal; too often it is the late symptom that brings the patient to the physician. Sometimes pain is insignificant; too frequently, it is a late manifestation of a disease that has already progressed beyond the hope of relief.

This Symposium has been prepared with the view of helping the physician to review his knowledge of this important symptom.

Lewis J. Pollock: HEAD PAIN: DIFFERENTIAL DIAGNOSIS AND TREATMENT.

Clarence F. G. Brown and Ralph E. Dolkart: ABDOMINAL PAIN: ITS SIGNIFICANCE TO THE CLINICIAN.

M. Edward Davis: PAIN ARISING FROM THE FEMALE PELVIS: DIFFERENTIAL DIAGNOSIS AND TREATMENT.

Eric Oldberg: PAIN ARISING FROM LESIONS OF THE NERVES AND SPINAL CORD: DIFFERENTIAL DIAGNOSIS AND TREATMENT.

Frederick W. Hark: PAIN IN THE MUSCLES, BONES AND JOINTS.

G. K. Febr: PAIN ARISING IN THE CIRCULATORY SYSTEM: DIFFERENTIAL DIAGNOSIS AND TREATMENT.

Robert S. Berghoff, Angelo S. Geraci and Donald A. Hirsch: THE RELIEF OF CARDIAC PAIN.

Walter R. Fischer: RELIEF OF PAINFUL FEET.

J. P. Greenhill: CONTROL OF PAIN IN CASES OF CANCER.



## CLINIC OF DR. LEWIS J. POLLOCK

FROM THE NORTHWESTERN UNIVERSITY MEDICAL SCHOOL

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### HEAD PAIN: DIFFERENTIAL DIAGNOSIS AND TREATMENT

INCLUDING the face and cranium, pain in the head may be a symptom of so many diseases that time would not permit even the naming of these diseases in this clinic. In general, however, such pains in the head, ordinarily interpreted as headache, which occur as a result of diseases not primarily involving the head may result from *endogenous* and *exogenous intoxications* (for example, carbon monoxide poisoning and uremia, respectively), from all *infectious diseases, diseases of the viscera* (gastro-intestinal tract, heart, lungs, liver, pancreas, etc.), *constitutional diseases* like gout, *diseases of the blood* (anemia, leukemia, polycythemia), *vasomotor disturbances, hypertensive arterial disease*, and numerous others. In such instances the other signs and symptoms of underlying disease are readily ascertained. In cephalic disease there may, in many instances, be no signs of general bodily disease and here some difficulty in diagnosis presents itself.

#### DIFFERENTIAL DIAGNOSIS

The first thing to do when confronted with the diagnosis of head pain is to determine whether it is *organic* or *functional* in origin, whether it is due to structural disease or to a psychological maladjustment as in neuroses. If it is of *organic* origin, it becomes necessary to determine whether it is of *intracranial* or *extracranial* origin, for example, whether it is due to a brain tumor, a ruptured cerebral aneurysm, or to fibrositis, sinus disease, etc. If it is of intracranial origin, is it due to cerebral or extracerebral disease; thus is it due to tumor, abscess of the brain, hydrocephalus, etc.; or leptomeningitis, acute or chronic, as tuberculous and syphilitic; or to disease of the dura, pachymeningitis hemorrhagica, late subdural hematoma, so-called spontaneous subarachnoid hemorrhage?

**Head Pain from Intracranial Tumors.**—In the majority of cases head pain or headache does not occur as the sole or principal symptom of intracranial disease. The following cases will illustrate this point:

*Case I.*—This seventeen-year-old girl entered the hospital because of severe headaches. Four years ago she fell, striking the back of her head, and was unconscious for three or four hours. She then remained in bed for one month. Four months later she developed diplopia and began to complain of severe occipital headaches which would appear and disappear suddenly. These have continued until the present time, and she has developed defective vision, a choked disk, with four diopters swelling appearing as long as three and a half years ago and then receding. When examined there was discovered a slight weakness of the left side of the face and left arm, somewhat more weakness of the leg, and x-ray evidence of increased intracranial pressure. She was operated upon by Dr. Loyal Davis and a papilloma of the choroid plexus was removed.

*Case II.*—A girl, five years old, was brought to the hospital with a history of attacks of vomiting preceded by headache, at first only after eating and then any time in the morning. The headache was frontal in location, quite severe and throbbing. After a period of vomiting it would at times suddenly disappear, but in the last three weeks it has been constant. Three months ago diplopia appeared and, three weeks ago, convulsive seizures began. On examination this child had bilateral papilledema, markedly diminished vision, stiffness of the neck and marked ataxia. Dr. Loyal Davis removed part of an extensive medulloblastoma of the cerebellum.

*Case III.*—A boy, eight years old, had a history of having fallen two and a half years ago from a height of 15 feet, striking the back of his head. A year later he fell 5 feet, again striking his head. Even preceding these falls the boy complained of headache and, during the last two months, they have been constant and associated with pain behind the eyes and stiffness of the neck. On examination he showed bilateral papilledema and ataxia of the trunk. Dr. Loyal Davis removed a medulloblastoma of the cerebellum.

*Case IV.*—A male adult, aged twenty-five, began to have headaches once a month; for the last five months they have become progressively more frequent and severe so that, for the two weeks prior to examination, they were of such intensity as to force him to go to bed. When he would lie on the right side the headache would abate for a time and then recur. The headache was increased by using his eyes, by straining or movement, and if he sat up it became associated with dizziness. Straining at stool so intensified the headache that he nearly fainted. The pain was localized to the left occipital region. On examination this patient had bilateral papilledema and nystagmus upward as well as on lateral gaze. A sarcomatous meningioma was removed by Dr. Loyal Davis.

*Case V.*—A fifty-three-year-old woman had shown peculiar signs of changes in personality and behavior for several months prior to admission. During this time she had experienced constant right frontoparietal and occipital pain. The pain was severe, sharp and knife-like, and was not relieved by acetylsalicylic acid though it was somewhat helped by heat. Associated with this pain was somnolence, lassitude and disturbance of vision. On examination

there was bilateral papilledema, slight weakness of the left side of the face, and dragging of the left foot on walking. A right-sided astroblastoma was found by Dr. Loyal Davis.

These cases illustrate that although headache may be the *presenting* symptom, it is not the *sole* symptom in intracranial tumors. Diplopia, hemiparesis, facial paresis, ataxia, loss of visual acuity, vomiting, reflex changes and mental disturbances were in all of these cases at times associated with the headache. Just as signs of increased intracranial pressure are not constant to brain tumor, so headache may be quite often absent. When it is present, other signs of intracranial disease can be found.

*Characteristics of Head Pain.*—Usually the headache is associated with vomiting, which may become projectile in character and usually does not lead to alleviation of the pain. Here the headache is a real pain; it is sharp and severe, and continuous. It may be a throbbing, stabbing, boring pain. It is often brought on by sudden changes of posture and may as suddenly disappear by changing the position of the head; at times, as in intraventricular and infratentorial tumors, the patient may hold his head in a position which tends to lessen the possibility of occurrence of the pain. It may be associated with suboccipital tenderness and rigidity of the neck. The pain is increased on jolting and straining and, with sudden exacerbations of the pain, vomiting may occur.

The *location* of the pain is not characteristic, nor is the location of the pain an index of the localization of the tumor. At times cerebellar tumors may produce occipital headaches—but so may frontal lobe tumors. The side upon which the headache occurs likewise does not indicate the side of the tumor. The headache often diminishes during the middle portion of the day and increases at night, and is frequently severe in the morning; it produces marked loss in sleep and at times awakens the patient from sleep.

The *character of the tumor* at times influences the type of headache and its severity. Rapidly growing tumors are associated with more headaches; hard tumors produce more marked pain than do soft ones; circumscribed tumors produce pain of greater intensity than do infiltrating tumors. Tenderness to percussion of the skull at times serves to bring out an area of circumscribed tenderness which may indicate the presence of intracranial disease.

In cases of *other intracranial causes* of headache it is also rarely found that headache is the sole symptom. Thus in the

following case of a thirteen-year-old child who had been ill with an upper respiratory infection, a left frontal, maxillary and ethmoidal sinus infection developed. She complained of headache but, in addition, there was elevation of temperature and leukocytosis. The headache persisted throughout the course of her illness, but she became irrational, somnolent, and developed a slight rigidity of the neck, papilledema, and then convulsions and weakness in the right side of the face. An abscess in the left temporal region was successfully drained by Dr. Loyal Davis.

*Associated Signs and Symptoms of Intracranial Disease.*—

As in the foregoing case of cerebral abscess, so in other types of pathology associated signs and symptoms lead to the diagnosis. The *hemiplegias* of sudden onset in hemorrhage, thrombus and embolism, the sudden onset of *excruciating suboccipital pain* with loss of consciousness, rarely hemiplegia, and *rigidity of the neck* characterize subarachnoid hemorrhage, usually due to ruptured cerebral aneurysm. Inflammation of the leptomeninges alone or along with encephalitis is associated with rigidity of the neck, *Kernig's sign*, *Brudzinski's sign*, and evidence of inflammatory disease is found in examination of the cerebrospinal fluid. Serous meningitis with paroxysmal hydrocephalus is characterized by the occurrence of definite attacks of headache, *vomiting*, sometimes *choked disks*, and signs of *interference with cerebral function*. Such attacks, after running a relatively short course, may disappear and a considerable length of time elapse before another occurs. Often one may in such cases obtain a history of other phenomena of anaphylaxis, as *angioneurotic edema* or *Ménière's syndrome*.

Most of the cerebral diseases produce some interference with function of motion, sensation, tone, synergy, speech, reflexes, and cranial nerves. No more than a consistent difference in the activity of deep *reflexes* upon the two sides may be noted, but when this is combined with diminished superficial reflexes on the same side, it is a strong indication of organic disease. Very frequently, and long preceding any change in the optic nerve, may be found changes in the *visual field*. Especially is this true in temporal lobe lesions where a *quadrantic anopia* and a headache may be the sole symptoms of tumor. Whether encephalitis uncomplicated by meningitis can produce headache cannot be stated. It is to be remembered that many of the encephalitides are associated with a meningitis and that in lead encephalopathy a marked change in

renal function may be present, which in itself may produce marked headache.

*Syphilitic* diseases of the brain and meninges are frequently accompanied by severe pain, not always increasing at night and never of the intensity of pain produced by such diseases of the cranium and periosteum. Syphilitic osteitis and periosteitis as well as those due to other causes are accompanied by tenderness to pressure and frequently edema of the scalp and periosteum. Often other evidences of syphilis are present and the Wassermann reaction is positive.

**Head Pain from Disease of Cervical Vertebrae.**—At this point mention might be made of the fact that diseases of the uppermost cervical vertebrae may produce severe occipital headaches, as may pachymeningitis hypertrophica cervicalis.

*Case VI.*—A woman, fifty-two years old, presented herself with headache characterized by pain extending from the back of the neck upward over the occiput, particularly to the right side and behind the right ear. It was a continuous pain, present all day, worse in cold weather, and was associated with marked tenderness in parts of the scalp, to such a degree that she could not adequately brush her hair. The pain did not awaken her, but if she awoke from sleep the pain was present.

Examination showed no evidence of organic neurologic disease nor any visceral disease. The tonsils were badly infected. She had an elevation of temperature, usually at midday up to 99.6° to 100° F., and a leukocytosis of 11,000. Over the posterior part of the skull were a number of areas over which pressure produced exquisite pain. These areas did not follow the distribution of a peripheral nerve.

**Neuralgia.**—Often pain in the head or certain types of headache are classified as neuralgia, *viz.*, auriculotemporal, occipital, etc., neuralgia. As is often the case when the pain is due to some undetermined underlying pathologic process, the term "neuralgia" or "neuritis" is invoked to describe the condition. This I believe is a mistake. If we will accept *trifacial neuralgia* as characteristic of the neuralgias, then sudden paroxysms of severe pain in the distribution of the sensory supply of the nerve, lasting only a fraction of a second, not more than a few, and brought about by touching a trigger or algigenetic zone, are seen only in relation to the trigeminal or glossopharyngeal nerve. Many of the so-called neuralgias of the head are instances of *rheumatic*, *indurative*, or *nodular* headache. The frequency of this headache appears to vary in different countries in direct proportion to its recognition. By some observers it is considered to be the most common form



of headache. It is certain that it is not a rare form. It is more common after the fortieth year of life, and perhaps is a little more frequent in women. It produces real pain, which is at times intense and at other times nagging. It is a continuous pain with intermissions, remissions and exacerbations. There are no definite paroxysmal attacks, and nausea and vomiting do not enter into the symptomatology as is the case with migraine. Like the pain of sinus disease, it is frequently worse in some one part of the twenty-four hours and may at times be limited to this period. Usually the location of the pain is occipital or suboccipital, and from this region it may radiate to the vertex, the frontal, or temporal, or to all of these regions. Of more significance is the presence of tenderness to pressure. This is not a superficial tenderness or "hair hyperesthesia" as occurs following migraine; nor is it a generalized tenderness of the skull, nor is the pain increased by blows to the head as is the case with sinus disease. The tender areas appear consistently in certain parts. They occupy the lower occipital and upper neck, particularly at the point of muscular insertions on the occiput, the occipital aponeurosis, frequently over the trapezius, and not rarely along the border of the squamous portion of the temporal bone. It is at these tender points that certain swellings or nodes have been discovered. Although it is claimed that these nodes can be readily felt, I must confess that my sense of touch is insufficiently developed to recognize them in but a small percentage of cases. Constant in these cases is a slight increase in temperature, ranging from 99° to 100° F., and a very slight leukocytosis. The differential diagnosis of this disease is at times complicated by the fact that it may be found associated with migraine and frequently has engrafted upon it a psychasthenic headache. Inversely, it is not rare to find a psychasthenic patient who develops an indurative headache which, due to the constitutional make-up of the patient, one is very prone to overlook.

It can be readily seen that indurative headache and migraine may be readily differentiated, and usually this may be said of sinus headache. Neither sinus nor indurative headaches are regularly paroxysmal. They last many days and there are no prodromata. The intensity of the pain in both increases at some definite period of the day, corresponding to increase in temperature. They are usually made worse by exposure to cold. They are not *per se* associated with attacks of nausea or vomiting. They are associated with definite evi-

dence of infection, and indurative headaches with localized tenderness to pressure.

**Migraine.**—A typical attack of migraine is readily recognized, but at times complications arise which make the diagnosis difficult. Thus a young married woman gives a history of having a father and two paternal uncles who suffered from migraine. At the age of nine she began to have headaches which were ushered in by a day or two of lassitude and immediately preceded by spots before the eyes; this condition rapidly increased in extent and form until a typical fortification type of scintillating scotoma developed. After thirty or forty minutes a headache began, usually over one or the other eye, and spread in extent and severity, and was followed after some hours by nausea and then vomiting. After a night's sleep the headache was absent. These phenomena recurred at regular monthly intervals until two years ago, when she began to have headaches which lasted, at times continuously, for as long as five weeks; at other times she was free from headache for as long as three weeks. Since she is only thirty-three years old it was thought unlikely that the protracted headaches were a continuation of her migraine. A bone cyst of the skull was discovered by x-ray study and this was removed by Dr. Loyal Davis.

Migraine is a *disease entity* and not a headache. Headache appears in the train of symptoms, but at times need not be present. The condition possesses one characteristic which is found in no other type of headache. It is *paroxysmal*. The paroxysms are separated by long periods of time, usually a month. Later in the course of the disease the headaches may occur as frequently as once a week, rarely more, but headaches which occur daily for a week or more are not due to migraine.

The common type, the *ophthalmic*, begins with disturbances of vision; a bright spot on one side of the fields slowly enlarges and spreads, darkening at the center and becoming angular and being followed, at times, by blindness in the scintillating area. After ten to thirty minutes the headache comes on and slowly spreads, usually affecting one side. It becomes intense after a few hours; nausea ensues, and at last ends in vomiting; and then sleep follows. When the patient awakens the pain has disappeared. Visual disturbances occur in about half the cases, but other sensory disturbances may occur, such as numbness of the extremities; in other cases there is dysarthria, aphasia, and even temporary weakness of the extremities. The headache is intense and continuous while it lasts; it is fre-

quently throbbing, increased by movement (in fact by any effort, mental or physical), or by stimulus of sound or light. It is associated with vasomotor phenomena of, at times, great pallor, at times flushing, and increase of sweating. When the pain is on it lasts no more than twenty-four hours. Migraine usually begins with puberty. It increases as age increases and disappears at the time of the menopause in women and a corresponding time level in men. During pregnancy such headaches frequently cease.

**Headache Associated with Neurosis.**—In a very large number of patients suffering from headache careful search reveals no organic disease. Such headaches may be termed "*psychogenic*" or perhaps better, headaches associated with neurosis:

A man, sixty-five years old, presented himself with unbearable headaches. These headaches appeared when, after stooping or bending, he straightened up, as after talking on the telephone, rising from a theater seat, and likewise following eating, chewing, writing, talking or concentrating. Close inquiry determined that it was not pain but a "feeling of beating, a feeling as if the neck needs grease, a pulsation, a thickness, and it is horrible." Neurologic examination failed to reveal any evidence of disease. A moderate hypertension was found, but renal function was normal. It is significant that on questioning the patient it was elicited that he felt that if the pain would continue he would either lose his mind or have a stroke.

Does a patient suffering from psychasthenic or neurotic headache mean that he has pain in the head when he complains of headache? Usually he does not. It is a feeling sometimes describable, at times not. Always it is "intense," "terrible," "horrible," "splitting," "awful," or "unbearable." Indeed it is the *hyperbole* and *exaggeration* which point these headaches out.

The sensations complained of are myriad. There is the classical *cásque* or helmet compression, the *clavus* or nail in the head. Patients complain of a "fulness," a "weight upon the head," a "bursting feeling," a "popping," "pins and needles," a "feeling of emptiness," a "dragging" or "throbbing," a feeling as if the head "contained liquid which changed its level with each movement," a "dripping" in the skull, a "feeling of floating," of "dizziness," "unsteadiness," a "beating of the brain," of "tension," of "heat," a "thickness," "prickling," "flickering," "unsteadiness" of the head, "pressure at the root of the nose," "freezing," and so on *ad infinitum*. The so-

called pain may involve any part of the head, but the *top* of the head is the place of selection, though the frontal, parietal, and occipital regions are frequently affected. The pain shifts from day to day or from hour to hour.

The pain or sensation is continuous; usually it is present on awakening in the morning, it is somewhat better for an hour after luncheon, and it is again intensified in the afternoon. It is usually unaffected by weather. It is usually not affected by ordinary change in position but is by jolting. It is not accompanied by nausea or vomiting. It is always increased by making decisions and always by work. It is relieved by reassurance, whether by a physician's statement or by favorable observation by the patient.

If the patient becomes interested in any pursuit, as long as this interest lasts the headache will abate. It is abated for some length of time by any new treatment or doctrine. It is worse in crowds, in theaters and elevated trains. Here again the factor of *fear* molds the character of this headache. The patient's discomfort is influenced by confusion. He is afraid that unless he holds on to himself he may fly off the handle, do something to attract attention, or create a scene; therefore, a crowd impresses upon him increased effort with ensuing fatigue. Thus the headache is increased by excitement, disputes, quarrels, and domestic, social and business conflicts.

As is the case with sensations relative to phobias relating to the heart or stomach, so with this headache. A real pain or discomfort of organic origin may often have preceded it and have disappeared, leaving the field to its elusive successor. It may follow a migraine, an indurative, ocular or sinus headache, or may co-exist with them.

The symptoms *associated* with the headache are of great importance and frequently produce greater disability than the headache itself. Prominent among these are depression, abulia, inattention, difficulty in concentration, forgetfulness, introspection, anxiety, fears, indecision, fatigue and insomnia. Peculiar to the insomnia of psychasthenic headache is that produced by fear of going to sleep lest something occur during slumber.

In the differential diagnosis of these headaches it is important to remember that not only is it necessary to distinguish them from organic headaches, but they may be the beginning of a more serious condition—a beginning melancholia, dementia praecox, or dementia paralytica.

## TREATMENT

**Headaches Due to Intracranial Lesions.**—A few words may be said concerning the treatment of some of these headaches. In the case of those produced by intracranial disease, *temporary alleviation* may be necessary pending operative treatment; or in the case of infectious disease, serum therapy may be used, and so on. It is not necessary to name the various analgesics which are useful; no one is more efficacious than another. It is necessary to point out the danger of using any which produces a *depression of the medullary centers* in cases of tumor, craniocerebral injury, and other cases with increased intracranial tension, such as abscess and hemorrhage. It may also be almost categorically stated that *opium* and its alkaloids are *contraindicated* despite the ineffectiveness of other measures, since the first consideration of treatment is not to injure the patient.

*Hypertonic solutions of sucrose*, injected intravenously in doses of 200 to 500 cc., give palliative results. *Magnesium sulfate* by mouth or by rectal drip is also useful. *Caffeine sodio-benzoate*, 0.5 gm. every four hours by mouth, likewise may be beneficial.

**Indurative or Nodular Headaches.**—The treatment of indurative or nodular headaches is very often successful, but persistence is necessary. After removal of the sources of infection, *heat*, and particularly deep, long-continued *massage*, is often followed by recovery. The massage must be given daily. For the first ten to fourteen days, it may produce an increase in the headache, but afterward the condition tends to ameliorate and disappear. Large doses of *salicylates* combined with *sodium bicarbonate* are useful. At times *nonspecific protein treatment* assists in reaching the goal.

**Migraine.**—In the treatment of migraine it is necessary to *exclude from the diet* such articles as may produce allergic reaction. Chocolate is a common offender and in many instances precipitates an attack. A regimen of an orderly life with avoidance of overwork, strain, emotional disturbances, with daily outdoor exercise and sufficient recreation and careful attention to proper elimination, is necessary.

For the continuous treatment directed to *prevention* of the seizures I have found two useful procedures. One is the use of the fluid extract of *cannabis indica*. It is prescribed with empty capsules and the patient is instructed to start with one drop after each meal. Each day it is increased until the patient experiences some subjective sensations, and then the dosage is dropped to three-fourths of that dosage and con-

tinued. From time to time the dosage is in the same manner redetermined. The treatment must be continued for some years.

Another method is the continuous administration of *sodium bromide*. I prefer to use it as in Bechterew's prescription:

Sodium bromide .....	1 oz.
Fowler's solution .....	1 dr.
Infusion of Adonis vernalis .....	q.s. ad 1 pint

The patient takes a tablespoonful three times a day after meals. From time to time a blood bromide determination is made, and the amount in the blood should not exceed 175 mg. per cent. Pigmentation of the skin and keratosis should be watched for as indicative of arsenical intoxication.

To terminate an attack, *ergotamine tartrate* given subcutaneously in doses of 0.5 cc. of an 0.5 per cent solution, repeated in three hours, is often beneficial if given at the beginning of an attack. Likewise the oral administration of 1 to 2 mg. of this drug three times a day has in some cases been useful.

Though sporadic reports of successful treatment by cervical sympathectomy have been received, these procedures seem useless and irrational to me.

**Headaches Due to Cervical Sympathetic Involvement.**—In some cases of headache associated with evidence of cervical sympathetic involvement, particularly narrowing of the palpebral fissure, lacrimation, flushing, etc., *histaminase*, or desensitization to histamine by daily administration of small increasing doses of the drug, has been reported to give relief.

**Neurotic Headaches.**—The treatment of headaches in neuroses may be said to consist of three parts: the general treatment of the *underlying neurosis*, the treatment of whatever *phobia* may be present, and the *adjustment of the patient* to the conflict or maladjustment immediately responsible for the symptoms.

There is no one method of treating these headaches. It is more the matter of the physician than the method. One who is eminently successful with one method with which he is familiar may fail with another, however touted as a panacea.

A warning may be indicated relative to the *indiscriminate use of the bromides*, which may produce hebetude and obtusion, which may be interpreted by the patient as evidence of insanity. Phobias may be removed by persuasion and suggestion. The adjustment of conflict is possible only after careful study of the patient's difficulties, usually learned by careful history taking.



## CLINIC OF DRS. CLARENCE F. G. BROWN AND RALPH E. DOLKART

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### ABDOMINAL PAIN: ITS SIGNIFICANCE TO THE CLINICIAN

ABDOMINAL pain is one of the most interesting diagnostic problems that a clinician can face and oftentimes the life or death of a patient depends upon one's ability to think clearly. Frequently diametrically opposite types of therapy are dependent upon the correct diagnosis. By simple enumeration the causes of abdominal pain run well into three figures, and a discussion of the problems in differential diagnosis is always most pertinent.

Diagnoses of rare forms of abdominal disease are always interesting and important to make, but, unless the particular disease is kept in mind, such diagnoses can never be made. For practical purposes, however, it is important to eliminate these infrequent possibilities, and this can be accomplished only by well ordered thinking. Too often the clinician is confronted by abdominal pain as an acute symptom, with the entreating stimuli of both patient and family for relief of the discomfort, forcing hasty decisions. The dangerous practice of relieving pain *without an adequate working diagnosis* allays not only the abdominal, but the physician's distress as well, giving a false sense of security and further confusing the diagnostic picture.

**Importance of the History.**—The inaccessibility of the abdomen to accurate physical diagnosis makes a carefully elicited history imperative. The doctor must efficiently ferret out his information and overcome his sensation of being "pushed around" by the demand "to do something." The neglect of thorough questioning may omit an important associated symptom, to which the patient has attached no significance and hence has neglected to mention.



One should, therefore, *routinely determine*: (1) the history of previous similar episodes of pain; (2) the time and *exact character* of onset; (3) the intensity and particular characteristics of the pain; (4) the distribution for localizing signs; (5) radiation or change in location; (6) relation to food intake, defecation, urination, menstruation, physical activity, posture, and respiration; (7) the presence or absence of associated signs or symptoms, such as nausea, vomiting, hematemesis, anorexia, constipation, diarrhea, melena, chills, fever, cough or dysuria; (8) a careful dietary history, which alone may make the diagnosis of food poisoning, or alcoholic or chemical gastritis. During this routine the doctor has a chance to "size up" the patient: some exaggerate symptoms, some minimize them, and some are simply examining the doctor.

**Mechanisms Producing Abdominal Pain.**—In order to utilize intelligently the story of pain obtained from the patient, a knowledge of the mechanisms capable of producing abdominal pain is fundamental. Pain in the abdomen may arise in any one of several fashions. *True visceral pain*, the majority of physiologists agree, does occur. It is not well localized, varies among individuals, and is for the most part of no value to one unfamiliar with his anatomy and therefore of no value for purposes of diagnosis. Secondly, pain in the abdomen commonly occurs when there is *irritation* of the *parietal peritoneum*. Such pain usually remains localized, is easily determined, and does not constitute an especial diagnostic problem. *Referred pain*, the third type of pain which may occur, is of the utmost importance and must be considered from both the standpoint of being pain referred to the abdomen from extra-abdominal sources, as well as being referred to a somatic point of reference from some intra-abdominal organ.

We shall therefore briefly review some of the important points of diagnostic value. To avoid reduplication, the subjects of localized and referred pain will be discussed as a unit for each of the particular systems considered. The best diagnostic clue in attempting to localize abdominal pain as to the organ involved frequently comes from the location of the *site of reference* of the pain. Although the presence of typical sites of pain reference is distinctly helpful and will be emphasized, their absence by no means should rule a condition out.

#### GASTRO-INTESTINAL TRACT PAIN

Many publications have appeared on this subject. One of the most complete discussions is to be found in a monograph

published by Chester Jones in 1938<sup>1</sup> who, with his co-workers, was able to reproduce referred pain experimentally by distention of various levels of the gastro-intestinal tract. Localized midline pain or discomfort was fairly consistently reproduced at a level depending upon the area of digestive tract stimulated. Rarely was a segmental distribution obtained and occasionally direct splanchnic pain was produced.

**Esophagus.**—This organ rarely produces abdominal symptoms. For the most part, the manifestations of disease occur as a sensation of substernal discomfort intimately associated with the act of deglutition. Occasionally *cardiospasm* may produce high epigastric discomfort, usually localizable just below the xiphoid process.<sup>1, 2</sup> *Esophageal strictures* may produce the same type of distress as is seen in patients with marked cardiospasm.

**Stomach.**—Rivers<sup>3</sup> found that 90 per cent of patients with *shallow gastric ulcers* had pain which was poorly localizable. Fifty per cent of patients with large ulcers had discomfort definitely localizable to the epigastrium; 90 per cent of patients with *perforating types* of gastric ulcer had pain in the left upper quadrant near the costal margin. With mesenteric involvement, involvement of the transverse colon or abdominal wall, pain was referred to the thorax or back. With involvement of the pancreas by a posterior perforating ulcer, almost all of the patients have pain radiating through to the back. As far back as 1893 MacKenzie described pain referred to the epigastrium in all but 5 per cent of 320 cases of proved organic disease of the stomach.<sup>1</sup> Frequent radiation of pain occurs through to the back or to the left chest over the distribution of the sixth and seventh thoracic nerves. Bloomfield,<sup>4</sup> Jones,<sup>1</sup> and numerous other workers have corroborated these findings. The acute manifestations of perforating ulcers are well known, and with ulcers located upon the posterior wall of the stomach the reference of pain *through to the back* is the important thing to be kept in mind. Movement of pain from high up in the abdomen or back to the lower abdomen is indicative of seepage of gastric contents down along the peritoneal gutter or through the folds of mesentery, if perforation has already occurred. The relationship of food intake to ulcer pain is less constant than is commonly supposed. Chronicity and periodicity, with intervals free from discomfort, are more significant criteria. The relief of pain by the intake of food or soda is not indicative of ulcer *per se* as is classically described. It is at best a vague clue and is present in innumer-

able conditions rather than being considered peculiarly pathognomonic of ulceration. In *neoplasms of the stomach*, pain does not usually occur until ulceration or pylorospasm is present.

*Hiatus herniae* should be considered in vague types of epigastric discomfort. If a history of postural relationship of pain can be elicited, there is a definite diagnostic clue, but in a large number of instances such herniae may be entirely asymptomatic. We have recently seen two cases of diaphragmatic hernia which were found following unexplained bleeding from the gastro-intestinal tract, all other findings being negative. In one instance no symptoms referable to the hernia could be obtained, and in the other careful questioning elicited a story of vague discomfort localized to the epigastrium which occurred irregularly upon assuming the recumbent position or upon bending over.

*Gastritis* as a cause of epigastric discomfort is again assuming its importance in the sphere of diagnostic possibilities. *Perigastritis*, as with periduodenitis, produces indefinite symptoms referable to the upper abdomen and is to be diagnosed by exclusion, with the only really positive objective finding being the presence of great changes in motility, as seen by roentgen study. *Pylorospasm* is the commonest cause of epigastric discomfort. The symptoms attributable to it are usually such things as feelings of fulness, heaviness, or burning sensations, all localizable to the epigastrium and "finger point" only in extent of distribution. *Polyyps* occurring in the region of the pylorus give no constant type of discomfort, but that which does occur is referred to the midline in the epigastrium and is due to pylorospasm.

**Duodenum.**—Pain arising from the first portion of the duodenum is referred to a small area in the midepigastrium. This is well established both clinically and experimentally. In twenty-four subjects in whom it was possible to place a balloon exactly in the duodenal cap following distention of the balloon, seventeen of the subjects, Jones reports, had pain referred to the midline in the upper and midepigastrium; three subjects felt pain through from the midepigastrium to the back at the same level. Distention of other portions of the duodenum with few exceptions produced pain in the midepigastrium until the lower portion of the duodenum was reached, where pain was still referred to the midline but in the high umbilical region. In several instances, following distention of the second portion

of the duodenum, pain was referred straight through to the back or around the right costal margin to the back.

*Duodenal diverticulum* produces an inconstant type of discomfort to which there sometimes is a postural relationship. Pain is increased with the taking of food and is greatest in an erect or sitting posture. According to Warren, in the majority of instances there is no pain.<sup>5</sup> *Chronic dilatation of the second portion of the duodenum* is seen with neoplasms of the pancreas. In view of Jones' experimentally produced back pain by distending this portion of the duodenum, it is interesting to speculate as to whether or not there is any relationship between the dilatation of the duodenum and the pain referred through to the back so commonly associated with pancreatic lesions. *Duodenal surging* accounts for vague upper abdominal symptoms. The diagnosis of this motility disturbance is made by the roentgenologist.

In differentiating midline epigastric pain of abdominal origin, one of the chief intra-abdominal causes with similar distribution is *acute cholecystitis*, in which condition there is midline tenderness, sometimes to a marked degree, extending from the xiphoid to the umbilicus. The latter is probably due to the pylorospasm which goes with it. Other conditions to be differentiated will be discussed later.

*Chronic pain* in the areas so far described gives one certain well limited diagnostic possibilities. The exact nature of the lesion can by no manner of means be determined by the history, physical findings, or both. The final diagnosis can be reached *only* after thorough study and with the assistance of the roentgenologist. *Acute pain* arising from the region of the stomach and duodenum usually is the result of ulceration with perforation. The diagnosis of the surgical abdomen must be made early and the value of a plain film of the abdomen for the presence of air under the diaphragm cannot be overemphasized. Many diagnostic pitfalls can be avoided through its use.

**Jejunum and Ileum.**—The small intestine is the most insensitive portion of the gastro-intestinal tract. Practically all of the pain sensations, regardless of the particular mode of origin, are referred to the region of the umbilicus and usually remain well localized in the midline. If epigastric pain occurs, it is usually due to a reflex pylorospasm. If there is involvement of the mesentery, as with a strangulated hernia, the pain tends to be dragging in character due to traction on the mesentery.

For the most part, small intestinal pain is *spasmodic, indefinite and cramping* in character. In distending the small bowel, Jones found that variations of several feet in the position of the balloon made no appreciable difference in the localization in individual subjects. Only when the terminal ileum was reached was there any noticeable tendency to deviate from the periumbilical and midline reference. Miller, Abbott and Karr obtained quite similar findings.<sup>6</sup> Occasional radiations to the back, epigastrium, both right and left, and suprapubic regions were obtained by both groups of investigators. With distention of the terminal ileum there were wider shifts in the sites of pain reference to points midway between the umbilicus and pubis in the midline, to McBurney's point, and to the right hypochondrium just below the costal margin.

The determination of the site of origin of pain arising from the small bowel constitutes a great diagnostic stumbling block in the absence of out-and-out obstruction or mesenteric thrombosis. This condition will be discussed later. Even after roentgenologic examination, it is difficult to make definite diagnostic statements concerning the small bowel. *Meckel's diverticulum* may mimic acute appendicitis, with the qualification that pain is referred to the umbilicus. If there are embryonal cell rests of gastric mucosa in the diverticulum, many gradations of pain can occur, all of which, however, are referred to the umbilicus and midline. The time factor of increased distress one and a half to two hours after meals is a helpful diagnostic clue. *Obstruction* due to *volvulus* or *intussusception* usually presents an acute picture, as is the case with *strangulated hernia*, as well as *strangulated internal hernia*, with all of the characteristic findings of intestinal obstruction. *Acute inflammatory lesions in the surrounding organs*, especially with salpingitis, may only give rise to spasmodic pain referred to the midline unless there is accompanying inflammatory involvement of the parietal peritoneum in which case there will be localized findings. The "violin string" adhesions associated with gonorrheal salpingitis conceivably could account for this by producing pylorospasm.

**Terminal Ileitis.**—The cicatrizing type of regional ileitis produces right lower quadrant distress similar to that of acute appendicitis. Usually there is more reference of pain to the umbilicus than is seen in the latter condition. There may be associated diarrhea. Although symptoms may develop suddenly, there more commonly is a history of slowly progressing discomfort which periodically becomes accentuated. There is a *benign form* of regional ileitis which we have observed and

which has been described by McMillan<sup>7</sup>; it is due to local irritation resulting from the backwash of large bowel contents through an incompetent ileocecal valve in the presence of a spastic colon. In most instances there is an accompanying cecumitis.

**Appendicitis.**—All variations from the commonly accepted sequence of appendiceal pain have been observed. Many of these variations are due to the differences which occur in the position of the appendix. In a *retrocecal* appendix attached to a high cecum, pain may resemble gallbladder pain or pain associated with disease of the right kidney. In a *long redundant* appendix floating free in the lower abdomen, pain may appear to be pelvic in origin and resemble acute salpingitis. *Ovarian cysts* with twisted pedicles and ruptured graafian follicles must be considered in the differential diagnosis.<sup>8</sup>

Characteristically there is localized pain in McBurney's area associated with rigidity of the abdominal wall. The referred pain associated with acute appendicitis is of two types, one being the result of the appendiceal-gastric reflex and is referred to the epigastrium. This is due to *reflex pylorospasm*. Reference to the *umbilicus* is the second type and is what one would expect on the basis of Jones' studies on the effects of distending the cecum. In some instances pain has been described as being referred along the distribution of the first lumbar segments down into the groin and tunica vaginalis. Rovsing has suggested differentiation of right lower quadrant pain due to appendicitis from referred right lower quadrant pain by the application of pressure to the area. If the pain is referred, pressure will cause it to disappear; if the pain is due to local causes, pressure will cause it to increase in intensity. This is the so-called *Rovsing's sign*. Peritoneal rebound tenderness is another important physical finding associated with acute appendicitis.

Although the point is controversial, most men believe that the *inflammatory* and *mechanical* types of appendicitis are to be distinguished from one another. In the latter case the symptoms are low grade, chronic, and may be responsible for reflex disturbances of the stomach outlet. In the former case there are frank episodes, either one or several, which point to an inflammatory process.

By and large, the diagnosis of appendicitis is considered to be easier than it actually is. If anything, the pain is more often *atypical*. The safest rule is to operate if reasonable doubt exists. *Periappendicitis* has been described by some writers

on the subject, but how much of an actual clinical entity this condition is is difficult to evaluate.

**Colon and Rectum.**—For most part, pain sensations arising from the large bowel are localized to the midline well below the umbilicus. Jones' observations indicated that referred large bowel pain is less localizable than referred pain elsewhere in the gastro-intestinal tract. In the cecum, in addition to midline pain between the umbilicus and the pubis, pain was referred to McBurney's point. At any site in the large bowel, pain referred to the epigastrium usually signifies pylorospasm. In the left half of the colon, in addition to the midline reference, pain sensations also occurred in the left lower quadrant.

In *rectal disorders*, pain tends to remain well localized. *Intussusception* of the ileum through the ileocecal valve may produce, in addition to the usual pain reference, pain in the right half of the abdomen, presumably due to traction on the mesentery of the ileum. *Irritable colon* is an important cause of vague abdominal discomfort. It may be associated with spastic constipation, diarrhea, or with neither. Associated reflex pylorospasm no doubt is largely responsible for much of the symptomatology. Irritable colon may mimic innumerable other conditions, such as peptic ulcer or gallbladder disease. Alleviation of distress by the use of a bland diet, regulation of bowel habits, and the administration of antispasmodic drugs serves not only for therapy but for diagnosis.

*Diverticulosis* occurs frequently after the fourth decade of life and sometimes earlier. This is a diagnosis that is made usually only by roentgen examination of the large bowel. *Diverticulitis*, the acute manifestation of the condition, is not an uncommon cause of an "acute abdomen" in the aged and may produce all of the manifestations of acute appendicitis or low-grade intestinal obstruction due to malignancy. The diagnosis is finally made only by the roentgenologist or after surgical intervention. *Inflammatory conditions* of the large bowel resulting from infection with any of the dysentery organisms or amebiasis are to be diagnosed by the characteristic manifestations of diarrhea and the isolation of the pathogen from the bowel wall after sigmoidoscopy. Many patients with amebiasis are constipated and in these cases the diagnosis is difficult. Pain with these conditions, as with ulcerative colitis, is not characteristic. Midline discomfort, cramping and intermittent pain, frequently associated with the act of defecation, are common but unfortunately not invariable findings.

## LIVER AND BILIARY TRACT PAIN

**Gallbladder.**—Pain associated with *cholecystitis* and *cholelithiasis* is classically referred to the area below the angle of the right scapula. In eight patients studied by Zollinger and Walter,<sup>9</sup> the stimulation of the common bile duct by means of an electrode left in the common duct catheter at operation reproduced postoperatively the same type of pain as was present preoperatively. The majority of patients had distress referred to the epigastrium and right upper quadrant. Four patients experienced pain radiating through to the back, and one had pain radiating to both right and left across the upper abdomen. Zollinger was not able to reproduce pain to the back or interscapular region similar to that in biliary colic by distention of the bile ducts. Bergh and Layne<sup>10</sup> studied the mechanism of pain reference produced by distention of the common bile duct in fifteen patients having T tubes in place following operation. Gradual distention of the ducts failed to produce pain, but pain did result from sudden distention. All fifteen patients experienced deep epigastric or right upper quadrant pain; in eight cases the pain remained localized and in the remaining seven, the pain was referred to the interscapular and right subscapular region. Associated with the onset of pain there also resulted abdominal rigidity, greatest in the right upper quadrant, and frequent discomfort on deep inspiration.

Kuntz<sup>11</sup> explains referred biliary tract pain upon the basis of distention plus spastic contracture of the biliary musculature. Afferent impulses arising from the biliary musculature traverse nerve fibers in the hepatic portal and reach the spinal cord through the splanchnic nerves. In animals whose livers have been denervated by cutting all nerves in the portal canal and gastrohepatic ligament, no pain was produced when the ducts were distended.

The clinical significance of *interscapular* and *right subscapular* pain in gallbladder disease is fully in accord with the experimental findings. In this connection it is of interest to note that even after cholecystectomy in individuals who have had pain referred to the inter- and right subscapular regions, an area of hyperesthesia will sometimes persist at the site of maximal pain reference. There are many well known clinicians who maintain that colic associated with calculi is the only significant type of biliary tract pain. In our opinion, however, functional disturbances play an important role in the production of biliary tract pain.



**Other Conditions Producing Liver and Biliary Tract Pain.**—Certain other intra-abdominal conditions may produce pain in the right subscapular region, notably *ruptured ectopic pregnancy* and *acute salpingitis*. Many patients who have what appears to be pain along the intercostal nerves should be carefully observed in order to make sure that they do not have gallbladder disease.

*Rapid enlargement of the liver associated with sudden right heart failure* is a frequent cause of right upper quadrant pain which many times is difficult to diagnose. This is well borne out in individuals having kyphoscoliosis with heart failure due to chest deformity. Right heart failure occurs in the great majority of these individuals, and abdominal pain is often one of the earliest symptoms. The hepatic parenchyma is insensitive to ordinary stimuli; the serous covering is also insensitive. Rapid enlargement and distention of Glisson's capsule produces a sensation of fulness and pressure in the abdomen, frequently with severe right upper quadrant pain. Kuntz believes that pulling down on the attachment to the diaphragm is also an important mechanism. Recently we saw a sixty-eight-year-old man, under our observation for a period of ten years, who had increasing coronary artery sclerosis. Upon suddenly going into auricular fibrillation, he presented an almost classic picture of acute gallbladder disease, the right upper quadrant pain, however, being due to sudden enlargement of the liver. Right upper quadrant pain due to hepatic enlargement with right heart failure occurring in the course of rheumatic heart disease is common. The associated feelings of nausea and fulness in the abdomen sometimes are confusing unless one is familiar with the mechanism involved.

#### RENAL AND GENITO-URINARY TRACT PAIN

**Kidney and Ureter.**—The kidney renal parenchyma is incapable of pain sensation. The capsule of the kidney is innervated by branches of nerves from the tenth, eleventh and twelfth thoracic segments. Distention of the capsule, renal pelvis, or ureter produces quite characteristic types of pain. The location of the ileo-inguinal and ileohypogastric nerves is such that distention of either the kidney capsule, pelvis, or ureter by pressure upon these nerves will produce pain referred to the areas of distribution: pubic region, inner aspect of thigh, and genitalia.

Usually pain from distention of the capsule itself, as with *cortical abscess*, is referred directly to the back, as is the case

with a *calculus in the renal pelvis*. This type of pain may be quite acute, is not as severe in character as that observed with ureteral colic, and is accentuated by deep inspiration or flexion of the spine. *Ureteral stone* characteristically produces severe intermittent pain referred to the groin and genitalia.

Perhaps more emphasis should be placed upon the great variety of pain distribution occurring with *renal calculus*. One of us has recently reviewed a group of 500 cases of proved renal calculus. The most common type of pain was a sharp, intermittent, colicky pain, or a constant but severe dull, aching pain in the costovertebral angle on the involved side. Pain may remain absolutely localized or may radiate: (1) to the flank; (2) to the inguinal region; (3) to the pubes; (4) to the genitalia; (5) to the right or left lower quadrant; (6) to the umbilicus; (7) to the epigastrium; (8) across the midline to the opposite side of the abdomen; or (9) to the costal margin. Bizarre distribution is common if bilateral calculi are present. To a certain degree the exact location of the calculus, whether in the renal pelvis or in the ureter, determines the type and extent of pain radiation.

*Renal tumors* are generally not associated with pain unless there is involvement of the capsule or distention of the ureter. In this connection, with the *passage of blood clots down the ureter*, the same type of pain distribution as seen with calculus may occur. We have recently seen one such case in which there was *renal apoplexy* associated with marked hypertension resulting from chronic pyelonephritis. *Torsion and blocking of the ureter*, Dietl's crisis, gives a similar picture to ureteral calculus. *Acute nephritis* may produce mild painful sensations referred through to the back which are probably due to distention of the capsule. Great care must be taken to differentiate right-sided renal colic and gallbladder disease.

*Renal infarcts* are not usually associated with pain. Occasionally with large infarcts, all modalities of costovertebral angle pain have been observed, associated with upper abdominal discomfort. Usually there is no reference.

**Other Genito-Urinary Organs.**—The bladder, skin of the scrotum, penis, mons veneris, and labia majora are innervated by the same spinal segments. Pain due to *bladder stone* and *acute retention* is referred to these areas and to the suprapubic regions. The close association between symptoms and the act of micturition does not make bladder pain a diagnostic problem.

## PANCREAS

*Acute pancreatitis* produces excruciating, paroxysmal, right upper quadrant pain radiating through to the back in the region of the ninth to eleventh thoracic vertebrae. Usually there is some preceding disease, such as duodenal or gastric ulcer, gallbladder disease, and occasionally *mumps*. The pain may occur after biliary tract surgery. The diagnosis is made upon the establishment of a predisposing factor, lack of relief of symptoms from morphine, signs of an acute abdomen, and presence of localized findings in the right upper quadrant. The presence of a marked elevation of blood diastase usually removes any question concerning the diagnosis. In this connection it is important to remember that the blood diastase determination must be made *early* because the values may return to normal limits or inconclusive levels after the lapse of several hours.

*Chronic pancreatitis* and *pancreatic cysts* usually produce mild discomfort referred to the epigastrium. *Pancreatic calculi* produce pain similar in intensity to that seen in acute pancreatitis. *Thrombosis of the pancreatic arteries* has been discussed by Connors, but no symptom picture can be correlated. *Neoplasms of the pancreas* do not produce pain of an acute type. Persistent pain radiating through to the back is a most important diagnostic clue. In too many instances it is used in retrospect after the diagnosis becomes obvious by more advanced findings.

ABDOMINAL PAIN DUE TO VASCULAR DISEASE WITHIN  
THE ABDOMEN

**Mesenteric Vascular Occlusion.**—Acute abdominal pain resulting from *mesenteric vascular occlusion* is a clinical entity occurring with greater frequency than is commonly supposed. Dunphy and his associates<sup>15</sup> have reported twelve cases of mesenteric vascular occlusion associated with arteriosclerosis in which there was a story of chronic recurrent abdominal pain over a period of weeks, months, to years prior to death. In all cases the autopsy findings seemed to indicate the mesenteric arteriosclerosis as the most plausible cause of the abdominal pain. In all instances there were varying degrees of associated coronary sclerosis, so that the authors were reluctant to draw too positive conclusions. Their evidence, however, indicates that vascular disease of the mesentery can produce abdominal pain in the absence of gangrene or peritoneal irritation. In one

characteristic case reported, there was apparently a progressive thrombosis associated with recurrent pain over a two months' period. The pain was not sharply localized at any time, did not radiate, and was not accompanied by muscular spasm or marked tenderness of the abdominal wall. At the time of onset of this pain, it was related to the intake of food; only later did it become constant.

Mesenteric thrombosis occurring as a complication of *cardiac disease* usually presents an acute picture associated with the signs of peritoneal irritation and gangrene of the bowel. Dunphy and Zollinger<sup>13</sup> state there is no pathognomonic syndrome of mesenteric vascular occlusion but, given a patient with severe abdominal pain not relieved by ordinary measures, a paucity of physical findings so that the picture is confusing and does not fit any of the usual surgical emergencies, a high leukocytosis and pulse rate with a relatively low temperature, abdominal tenderness (more or less generalized), and evidence of a gastro-intestinal disturbance manifested by either vomiting or diarrhea (or by signs of subacute obstruction), and mesenteric thrombosis is a likely possibility.

**Intra-abdominal Apoplexy.**—Intra-abdominal apoplexy or spontaneous rupture of an arteriosclerotic artery of an abdominal viscus is a comparatively uncommon entity. In 1931 Green and Powers<sup>14</sup> reported one such case from the Peter Bent Brigham Hospital and summarized five others previously recorded in the literature. In 1935, Thompson and Dunphy<sup>15</sup> reported another case from the same hospital and, in the intervening years, two additional cases were reported by Mourgue-Molines and Cabanac.<sup>16</sup> In both of the Brigham cases there was acute onset of abdominal pain, diffuse in character, associated with vascular collapse. Surgical exploration in both instances revealed the gastrohepatic omentum filled with blood and clotted blood present in the abdominal cavity.

**Periarteritis Nodosa.**—Periarteritis nodosa is likewise an uncommon cause of abdominal pain, but the condition is interesting to consider. Whether the pain mechanism is the result of rupture of one of the small aneurysmal dilatations or due to infarction, especially of the spleen, cannot be determined. One of us has recently seen a case of well established periarteritis nodosa in which the diagnosis had been made in 1935. The history was punctuated by two episodes of acute abdominal pain, fever, nausea and vomiting. On the first occasion the patient reported that the symptoms disappeared without special therapy after about five days. On the second

occasion, which was the reason for a hospital admission, there was a similar story. Physical examination of the abdomen showed diffuse tenderness, moderate muscle spasm, some peritoneal rebound tenderness, but no localizing signs. The spleen was enlarged down to the level of the umbilicus and was tender. All manifestations, including the fever, had subsided by the end of three to four days.

**Splenic Infarction.**—Splenic infarction *per se* is commonly said to be a source of abdominal pain. We believe that this is relatively uncommon unless the infarcted area is of considerable size. In such instances pain is felt in the back at the level of the tenth, eleventh and twelfth ribs. If radiation of the pain takes place, it is generally to the left. In general, embolic infarctions may give a distinct symptom picture, whereas infarctions due to thrombosis are difficult to recognize.

**Dissecting Aneurysm.**—Dissecting aneurysms commonly produce pain in the chest, radiating through to the back. Recently we have seen one case in which the symptoms first appeared in the abdomen, with dissection of the aorta beginning at the bifurcation of the abdominal aorta.

#### ABDOMINAL PAIN ASSOCIATED WITH DISEASE OF THE UTERUS AND ADNEXA

The ovaries and testicles are innervated by segments of the tenth to twelfth thoracic nerves. The parenchyma of both are insensitive. Pain sensations arise from the peritoneal surface of the ovaries and from the tunica vaginalis of the testicle. Pain sensations from both of these areas may be referred to the lower abdomen and groin. During the period of ovulation a certain number of women experience *mittelschmerz* due to rupture of a follicle and exudation of blood into the abdominal cavity. Pain is referred to the side on which ovulation occurs and should always be considered in mild pain experienced in the middle of the menstrual cycle.

**Ovarian cysts** with a twisted pedicle produce acute abdominal pain localized to the side of the disease process and associated with localized tenderness, distention, rigidity, fever, leukocytosis and, sometimes, vascular collapse. With *dysmenorrhea*, there may be cramping suprapubic pain referred through to the lower part of the back plus the symptoms and findings of irritable colon. *Acute salpingitis* produces a symptom complex similar to that of acute appendicitis, especially if the right side is involved. The condition should always be considered in the differential diagnosis of right lower quadrant

pain in the female. Recently we have seen a case of right lower quadrant pain with marked tenderness in the right fornix in which the pathologic diagnosis was *tuberculous salpingitis*. Acute pain due to this cause is relatively uncommon. *Ruptured ectopic pregnancy* produces sudden, severe pain in the lower abdomen, and usually pain referred to the right shoulder. The latter is probably the result of diaphragmatic irritation.

#### ABDOMINAL PAIN OF INTRA-THORACIC ORIGIN

More commonly in children but also in adults, acute abdominal pain may be a cardinal symptom associated with an *acute sore throat, follicular tonsillitis, scarlet fever*, or any of the *exanthems*. Nausea and vomiting are common manifestations and abdominal tenderness is frequent.

*Lobar pneumonia* is the most frequent intrathoracic cause of abdominal pain. The early onset of a pneumonic process, especially if ushered in with nausea, vomiting and abdominal tenderness, may focus the entire attention to the abdomen. Many times before frank signs of consolidation appear, only the most careful of physical examinations will reveal the pneumonic process in the chest. If doubt exists, a chest film should always be taken. Abdominal pain and tenderness associated with pneumonia is usually greatest in the upper abdomen, and the muscle spasm is on the side of the involved lung. In pulmonary disease, pain reference to the abdomen is usually the result of irritation of the peripheral portions of the diaphragm which are supplied with afferent fibers from the lower six intercostal nerves, thoracic seventh to twelfth. In *diaphragmatic pleurisy* there may be true tenderness and rigidity of the upper abdomen.

*Pulmonary infarction* may begin with sudden onset of pain in the lower chest, substernal region and upper abdomen. In the cases reported by Ballinger,<sup>17</sup> the pain was oftentimes indistinguishable from that associated with myocardial infarction, though it was usually associated with more dyspnea, cyanosis and collapse. A history of recent injury, fracture, thrombophlebitis, or operation is significant. One of Ballinger's cases occurred after a Potts' fracture and there was a negative cardiovascular history.

*Coronary thrombosis* frequently produces abdominal symptoms associated with nausea and vomiting. The signs of vascular collapse, and the blood pressure and electrocardiographic findings, are essential in the differential diagnosis. The relationship of the symptoms to effort is important, as is

also any previous history of constricting substernal discomfort on exertion.

*Spontaneous pneumothorax* has been reported by Stiegmänn and Singer<sup>18</sup> to be associated with severe upper abdominal pain simulating an acute abdomen. The pain is more marked and persistent if there is associated hemorrhage into the pleural cavity. A coronary thrombosis is always carefully considered in the differential diagnosis, but when thinking of these conditions, it is essential to defer surgical intervention for the supposed abdominal disease.

#### ABDOMINAL PAIN AS A MANIFESTATION OF SYSTEMIC DISEASE

*Herpes zoster*, whether involving either the thoracic or abdominal segments, may be the cause of severe abdominal pain with marked tenderness and hyperesthesia. In the pre-vesical stage the diagnosis is difficult to make. The distribution of the hyperesthesia along the course of a nerve trunk is the best diagnostic clue.

*Diabetic coma* may be characterized by marked abdominal tenderness in the precoma phase. When associated with nausea and vomiting and gastric distention, as is so frequently the case, the question of an acute abdomen often arises.

*Gastric crisis* of tabes dorsalis always merits consideration, and the absence of knee and ankle jerks plus the other characteristic findings suggest this possibility.

*Lead poisoning* is now less common than previously since its recognition as an industrial hazard and the subsequent use of adequate measures to prevent it. The abdominal pain associated with lead colic is not localizable, and tends to be diffuse and cramping in character. More than any other cause of colicky or cramping abdominal pain, the pain of lead colic is relieved by pressure upon the abdomen.

#### MISCELLANEOUS CAUSES OF ABDOMINAL PAIN

*Arachnoidism* characteristically gives rise to acute abdominal pain with all of the signs of peritoneal irritation. There is usually no localized tenderness. One such case of black-widow spider bite with the signs of an acute abdomen has been reported by Kambosseff.<sup>19</sup>

*Torsion of an epiploic appendage* causing acute abdominal pain has been reported by Micheli.<sup>20</sup> Such a diagnosis can be made only at the operating table.

*Spine injuries and spinal cord tumors* may produce abdominal pain sufficiently severe to suggest a surgical abdomen. Careful histories for traumatic incidents are important and, if doubt exists as to the presence of bone injury to the spine in an atypical case, roentgenograms of the spine should be taken.

*Hysteria* may mimic all manifestations of an acute abdomen, and the absence of evidence of fever, leukocytosis, or constant physical findings after careful observation tends to suggest this diagnosis. An experience such as caring for a patient with encephalitis—*without* objective findings and yet with the death of the patient—indicates that careful observation must be used before proclaiming the process as functional. In the foregoing case, an out-of-town physician phoned to ask if the patient could die from functional nervousness. The postmortem examination showed encephalitis.

#### COMMENT AND SUMMARY

Obviously to rule out each of the numerous causes of abdominal pain at the bedside is both a practical as well as an intellectual impossibility. If the patient is complaining of some chronic form of abdominal discomfort, not punctuated by any acute episode, despite the host of diagnostic possibilities which come to mind one has adequate time to study the disease thoroughly and systematically, obtain what laboratory assistance may be required, and arrive at a diagnosis after a period of observation.

Acute abdominal pain is to be regarded as a medical emergency and an immediate diagnosis is imperative. The immediate issue which always must be decided is, *does this patient have a surgical abdomen?* The signs of a ruptured viscus, peritonitis, intestinal obstruction, etc., are fairly typical. When in doubt, surgical consultation, if available, should be sought immediately.

The importance of fever, an elevated white blood count, or polymorphonuclear increase in favor of an inflammatory process should not be neglected, keeping in mind that these reactions in elderly patients are often absent. The value of a plain roentgenogram of the abdomen for determining the presence or absence of dilated loops of bowel, elevation of one or both halves of the diaphragm, air under the diaphragm, or perhaps a gallbladder or renal calculus, cannot be overemphasized and this procedure should *always* be carried out when one is confronted by an acute abdomen and an indefinite diagnosis. No examination is complete, even though the diagnosis



may appear obvious, until the urine, and especially the sediment, has been studied.

In examining a patient with an acute abdomen, the examination should include determination of the tonus of the abdominal wall, comparison of the rigidity of the two halves of the abdomen, localized tenderness, peritoneal rebound tenderness, auscultation to determine the presence or absence of peristaltic sounds or whether they are hyperactive, search for herniae, rectal examination and pelvic examination. Such laboratory examinations as have been mentioned are important. Roentgen films, however, for the most part are available only if a patient is hospitalized. White counts and urine examinations are always possible.

If doubt persists despite all possible sources of assistance, careful observation of the patient over a period of hours, re-checking physical findings, repeating white counts and urinalyses, and taking repeated temperatures may yield sufficient additional information as to make a diagnosis possible. The time spent in waiting can well be used in the necessary preparation of the patient with such measures as clysis or intravenous fluid, gastric aspiration, or Wangensteen suction, as indicated.

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### PAIN ARISING FROM THE FEMALE PELVIS: DIFFERENTIAL DIAGNOSIS AND TREATMENT

PELVIC pain as well as pain in the lower abdomen and back is usually ascribed to the reproductive organs by women. These structures may become sufficiently altered by disease to produce pain, but a most careful examination of the environmental viscera should be included in the differential diagnosis of pelvic distress. There was a time when the ovary was regarded as the seat of all evil, and any discomfort that could not be accounted for in any other way was relegated to it. Numerous unnecessary surgical procedures resulted in which the ovary was removed or seriously mutilated. Fortunately, experience has decreased the number of surgical interventions of this type.

Pain is a *variable* symptom, depending in its character, severity and reaction on the individual patient and her threshold level for discomfort. Unbearable pain to one woman may provoke little discomfort to another. The woman who is occupied, perhaps busily earning her own livelihood, may complain less of minor aches and pains that become of monumental importance to the patient who has much leisure time which is not interestingly occupied. Fleeting pains are likely to provoke less response than a constant ache or discomfort or a pain which recurs from time to time. The general well-being of the patient will alter the reaction to pain at any given time. Thus, the healthy well nourished woman may pay little attention to some discomfort that the ailing patient finds unbearable. Pain, being a symptom and elicited from the patient, is so variable in importance that its proper evaluation may often be difficult, particularly in the absence of sufficient pathology to account for it. However, one must be careful not to *dismiss* pain as

unimportant because examination does not reveal a cause, nor must one undertake *radical interventions* in an attempt to explain and remove the origin of the pain. Continued observation of the patient, perhaps over a period of time, will ultimately uncover the significance of the pain. Many needless surgical procedures are undertaken for the relief of pain without a careful examination of the patient.

Pelvic pain is most often somatic pain produced by a local stimulus applied to the parietal peritoneum. The pain associated with inflammations of the adnexa is the result of the associated inflammation of the peritoneum. In ectopic gestation, the pain is usually produced by the escape of blood into the peritoneal cavity from the ostium of the tube, although there may be some mild discomfort as a result of the distention of the fallopian tube and its serosal covering. The pain may be localized to the region over the diseased organ or it may be referred to some distant focus. Free blood in the peritoneal cavity may accumulate beneath the diaphragm and produce referred pain in the region of the shoulder.

**Pelvic Pain of Sudden Onset.**—The sudden onset of pain in the pelvis is usually associated with some acute pelvic or lower abdominal condition. The clinical history and findings usually lead to the correct diagnosis, though at times the differential diagnosis may be difficult. It is important to remember that *continued observation* may aid in the diagnosis without seriously jeopardizing the best interests of the patient.

The following case history is quite typical:

*Case I.*—Mrs. M., aged twenty-six, entered the Chicago Lying-in Hospital on January 26, 1940. Her chief complaint was pain in the lower abdomen for the preceding twenty-four hours. Her menstrual periods had been regular, and the last period had ended on the first day of her present illness. She had been married for a year but had had no pregnancies. The pain began rather suddenly and was continuous in character. She was nauseated but did not vomit. On careful questioning she told of an attack of dysuria and frequency about a month prior to this present illness. She had not consulted a physician.

Examination revealed a young woman who was acutely ill. Her temperature was 38.6° C. and her pulse, 120. The lower abdomen was markedly rigid and exquisitely tender. The pain was no more intense at McBurney's point than at other levels. Pelvic examination revealed nulliparous external genitalia. The urethral orifice and the glands of the urethra were injected. Smears and cultures for gonococci were made. The cervix was clean. The corpus could be palpated with difficulty owing to the fact that the patient was splinting the abdominal wall. However, movement of the uterus caused pain and this pain was equally severe in moving the uterus away from the right and the left sides. No obvious adnexal mass could be outlined, but there was a sensation of fulness and intense pain could be elicited in both adnexal regions. A white blood count revealed 20,000 leukocytes.

## ACUTE PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease is the most common cause of pain in the lower abdomen, and chronic residual pelvic inflammation of the reproductive structures may provoke pain over a period of years until it is finally relieved by surgery. In the foregoing history, the differential diagnosis of all the conditions which may cause acute lower abdominal pain must be considered. However, acute salpingitis and appendicitis usually must be differentiated for the treatment of these two conditions is entirely different.

**Differentiation of Acute Salpingitis and Appendicitis.**—The onset of acute salpingitis is usually at the end of a menstrual period. The changes in the endometrium associated with menstruation are conducive to a spread of a lower genital tract infection into the fallopian tubes. It may be possible to elicit a history of lower genital tract infection with its urinary tract involvement. An attack of dysuria and frequency is particularly significant. The onset of a purulent vaginal discharge may help to establish a diagnosis. A history of sexual exposure in an individual who is unmarried may be of some value, but in our experience this phase of the history is most unreliable. In *acute appendicitis*, the patient may give a history of previous attacks of lower right quadrant pain.

The *pain* in acute salpingitis is usually limited to the lower abdomen. It is present constantly and is greatly aggravated by movement of the body. Palpation of the lower abdomen usually reveals rigidity and tenderness over both lower quadrants, although it may be more marked on one side. Acute pelvic inflammatory disease involves both adnexa. Abdominal tenderness, rigidity and pain limited to the region of McBurney's point is likely to be the result of appendicitis, as is nausea and vomiting.

The *general reaction* to the inflammation is much more severe in acute salpingitis than in appendicitis. In the former, an intense pelvic peritonitis develops very rapidly, involving all the organs in the pelvis. The temperature is likely to be higher, the white count may be higher and the sedimentation rate more rapid. The character of the general response to the disease may be of some help in establishing a diagnosis, but it must not be considered diagnostic.

A diagnosis may often be established on *pelvic examination*: If the uterus and adnexa can be easily palpated, and moved from side to side with little discomfort, the reproductive tract can be dismissed as the seat of the inflammation. Bi-

lateral adnexal tenderness with or without the presence of masses is usually indicative of salpingitis. An inflammation of the fallopian tubes must necessarily result in the involvement of the areas contiguous to the uterus. Movement of this structure may be restricted and certainly painful. One must remember that the appendix may become secondarily involved in an acute inflammation of the adnexa, so that it is not surprising to find pain, rigidity and tenderness over the appendiceal region.

It is important to establish a diagnosis of appendicitis *early* in the course of the disease for prompt surgical intervention is necessary.

**Treatment of Acute Salpingitis.**—Acute salpingitis is now being treated by chemotherapy. The sulfonamides are very efficacious in the treatment of gonorrheal infections. *Sulfanilamide* and *sulfapyridine* can be used, the latter drug being probably more effective. The present regimen consists of therapy over a six-day period, administering 3 gm. per day on the first two days and 2 gm. per day on the following four days in doses of 0.5 gm. The usual safeguards should be exercised. It is well to obtain a daily blood level and blood count.

It is possible that the early institution of therapy may result not only in the death of the organisms, but in the complete subsidence of tissue changes so that the structures rapidly return to the normal. However, the disappearance of living organisms is not necessarily followed by complete retrogression of pelvic pathology. Exudates in the pelvis and adnexal masses usually undergo slow absorption and residual changes in the pelvic organs may remain to harass the individual for years. It will require many years of experience to determine if chemotherapy will decrease the hazards of these residual changes which often necessitate major surgical procedures.

#### CHRONIC PELVIC INFLAMMATIONS

Chronic residual pelvic inflammations are the most common causes of chronic pelvic pain. These may arise as the result of gonorrheal infection, postabortal infections and, more rarely, tuberculosis. The increased incidence of abortions has resulted in a greater frequency of pelvic inflammatory disease, for this is the most common sequel of criminal abortion. The remote residual changes may not be evident at the time of the interruption of the pregnancy but may develop weeks after-

ward. The patient may appear to have enjoyed an uncomplicated abortion and later develop chronic pelvic pain.

The pathology of chronic pelvic inflammations differs according to the organisms responsible for the condition. In *gonorrheal salpingitis*, the infection has ascended from the lower genital tract so that the tubal mucosa is primarily involved and bears the brunt of the infection. Huge pus tubes or tubo-ovarian abscesses result. At times the tube becomes grossly distended by a clear fluid forming a hydrosalpinx. The adnexa remain adherent to abdominal viscera, but they can usually be separated by blunt dissection without injury to these adjacent structures. More rarely, the fallopian tubes are altered only moderately and appear as thickened, indurated, adherent structures.

The *pyogenic type* of pelvic inflammation usually involves the serosa and wall of the fallopian tube and less often the mucosal lining. These structures are not likely to be converted into large pus tubes or into huge hydrosalpinges but usually remain as indurated, thickened, adherent adnexa. The environmental structures may become more extensively involved, so that parametrial exudates are common and the uterus and its adnexa may become firmly fixed in the pelvis.

*Tuberculous salpingitis*, which occurs in 5 per cent of these pelvic inflammations, is most often secondary to a focus elsewhere in the body. The diagnosis is rarely made prior to the removal of the involved structures. Grossly, large tubo-ovarian masses may be present in which caseous material can be seen. More often one finds tubes that are thickened and unusually elongated, with the fimbriated ends still patent. The pelvic organs may be secondarily involved in the presence of a tuberculous peritonitis. Chronic pelvic inflammation in a tuberculous individual may be of tuberculous origin.

The *pain* in chronic pelvic inflammation is persistent; it is usually over one of the lower right quadrants but occasionally it manifests itself in the form of low back pain. It is usually aggravated during the premenstrual and menstrual periods. It is made worse by exercise and work which necessitates standing over long periods. It may be associated with dyspareunia, and is often made worse by coitus. The pain is rarely excruciating, but it soon wears the patient down by its constancy for the remissions are not long enough to allow the individual to recover. Adjacent organs may be involved as a result of adhesions, causing symptoms referable to these organs. Vesical and gastro-intestinal symptoms are the most frequent. The



patient may become a chronic invalid, a serious problem to her family, and ultimately a medical cripple as a result of unsatisfactory medical treatment.

**Diagnosis of Chronic Pelvic Inflammation.**—The diagnosis of chronic pelvic inflammation is not difficult in the event that there is sufficient pelvic pathology to be evident on bimanual examination. The adnexal masses, the tenderness that a pelvic examination provokes in these diseased structures, and the restriction of mobility on the part of the pelvic organs are quite characteristic. The diagnosis becomes more difficult in the absence of palpable pelvic pathology sufficient to account for the pain. In these women a painstaking and detailed history, several pelvic examinations at varying intervals, and continued observation may clear the diagnosis. The fluoroscopy and the x-ray may provide some additional information. These are the young women in whom it is better to *procrastinate* by resorting to all therapeutic expedients short of surgery. It is so easy to perform laparotomy, and then find little gross alteration in the pelvic organs, remove a fallopian tube and a portion of an ovary, and thereby start the young woman on a surgical career which will only end when all her reproductive organs have ultimately been sacrificed. There is no condition that demands greater patience in its management, greater resourcefulness, and more nicety in judgment than chronic pelvic inflammatory disease.

**Treatment.**—The treatment of chronic pelvic inflammation depends on the *extent* of the disease, the *disability* produced, and the *age* of the patient. Acute inflammations should be managed with great care to reduce the residual pelvic pathology. *Chemotherapy* should be resorted to early in the course of the disease. The subacute stage of the inflammation may require long periods of *rest in bed* and measures directed to maintaining the general physical condition of the patient. *Sexual rest* is likewise important during this period for coitus may produce exacerbations of an existing inflammation or reinfections from the original source. *Heat* applied locally to the reproductive organs by prolonged hot douches, Elliott treatments and diathermy, serve to hasten the retrogression of the inflammation and to minimize the resultant chronic residual changes. The use of hot water or hot air in a rubber balloon introduced into the vagina and carefully regulated as to temperature and pressure has provided an ideal method of applying heat to the pelvic structures.

In the *chronic stage*, the same therapeutic measures can be

used. These should be continued as long as they provide relief. Surgery should be resorted to when all other measures fail and the patient is incapacitated. Conservative management should be given a most thorough trial in *young women*, for in such individuals operative intervention usually means the sacrifice of most of their reproductive organs. The removal of a tube or both tubes and part or all of an ovary usually fails to cure the patient, and these incomplete operations pave the way for further surgery. In a large gynecologic clinic much of the surgery consists of re-operating on women who have had previous interventions for pelvic inflammatory disease. Surgical interference in the young woman should be postponed as long as possible and, when it finally becomes necessary, it should usually consist of the removal of both adnexa and the corpus of the uterus. In women *at or near the menopause*, one need not be so conservative for the removal of the pelvic organs does not entail so great a loss.

*Elliott treatments* occasionally produce an increase in the severity of the pelvic discomfort so that they cannot be tolerated. It has been our experience that most of these women suffer from an endometriosis of the pelvis and not from pelvic inflammatory disease. This unusual response to heat treatment is so striking that we have used it as a diagnostic aid in the differential diagnosis of endometriosis.

### ECTOPIC PREGNANCY

Ectopic pregnancy must likewise be considered in a differential diagnosis of acute lower abdominal and pelvic pain. The following history is rather typical of this complication:

*Case II.*—Mrs. V. S., aged thirty-two, Unit No. 103730. The patient was admitted to the Chicago Lying-in Hospital on the evening of July 14, 1940. Her last normal menstrual period began on May 15. The onset of her next period should have occurred about June 10. On June 17, approximately a week after her menses were due, she began to spot, and she continued to spot intermittently until the day of her admission to the hospital. During the preceding ten days she complained of lower abdominal pains which were fleeting in character. But an attack of pain was severe enough on July 10 to require a sedative before the patient could fall asleep. Intercourse the next evening was followed by a gush of dark blood.

On the afternoon of July 14 the pain in the lower part of the abdomen recurred and was much more severe than on previous occasions. It was generalized over the entire abdomen but was most marked in the left lower quadrant. The patient went to the bathroom about 7:30 P.M. and fainted. On being revived she vomited. At this time she first noted that the abdominal pain was relieved but that the pain had shifted to her right shoulder. She

continued to complain of the shoulder pain much more than of her lower abdominal pain. A moderate amount of dark blood escaped from the vagina.

The past history was of interest because of several facts: The patient's first delivery was complicated by a Bartholin's gland abscess which had had to be incised. Four years later, in 1938, she had had a spontaneous abortion for which curettage had been performed. She had subsequently developed pelvic inflammatory disease with concomitant bilateral adnexal masses of considerable size. Prolonged periods of rest, and heat in the form of vaginal douches and Elliott treatments, had resulted in a considerable retrogression of this inflammatory process.

On admission to the hospital the patient showed evidence of serious exsanguination. The mucous membranes were very pale, her pulse was 110, the blood pressure 90/60, and the temperature, 37.2° C. There was tenderness over the entire abdomen, which was most marked over the left lower quadrant. On vaginal examination the cervix was softened and bluish and the vault of the vagina was somewhat distended. Bilateral adnexal masses could be palpated, but the most of the tenderness was localized on the left side. The uterus was enlarged to the size of a five or six weeks' gestation and was softened. Laboratory findings of significance were: hemoglobin, 8 gm.; cell volume, 26 per cent; W.B.C., 26,000; and urine, negative.

Laparotomy was performed immediately and a left tubal gestation removed. The tubal wall had ruptured as a result of the chorionic invasion and destruction. About 1500 cc. of blood was present in the peritoneal cavity. A blood transfusion of 800 cc. was given during the operation.

If there had been any question about the diagnosis one could have resorted to puncture of the cul-de-sac. This procedure would have been easy to carry out and the result would have been confirmatory.

A careful and detailed *history* is significant in establishing a diagnosis. In 80 to 90 per cent of patients who have tubal gestations there is a history of a missed menstrual period. A week or two after the patient should have menstruated, she begins to have a bloody discharge, usually small in amount. This story is so typical that every patient who bleeds irregularly after a missed menstrual period must be carefully observed. The blood usually fails to clot. It is the result of a separation of the ectopic decidua in the uterus.

The *pain* may be cramplike and intermittent. It is usually the result of peritoneal irritation produced by blood escaping through the ostium of the tube from minute separations of the chorionic vesicle from the uterine wall. There may occur a sharp stab in the side when the patient exerts herself on sudden stooping or reaching for something. Often a sudden rupture of the fallopian tube occurs when the patient is in the bathroom. These fleeting pains and the bloody discharge may bring the patient to a physician for examination before gross changes have taken place.

*Tubal abortion or tubal rupture* is usually heralded by sud-

den excruciating pain in the lower abdomen. The pain has been described as stabbing or lancinating in character. In tubal abortion the pain may be colicky, resembling that of severe dysmenorrhea, but as blood accumulates in the peritoneal cavity, it loses this intermittent character. The pain in perforation of the tube occurs suddenly, and is intense and unbearable. The pain is produced by the extreme tension of the peritoneal covering of the tube and its sudden tearing with the escape of blood into the peritoneal cavity. Following the escape of the gestational sac through the rent in the tubal wall or through the ostium, the acute agonizing pain suddenly ceases. The patient experiences a sense of relief, although a dull discomfort persists in the abdomen. The patient may now develop shoulder pain, usually on the left. This is referred pain resulting from the accumulation of blood under the diaphragm. This *shoulder pain* is exceedingly characteristic of intraperitoneal bleeding and its appearance should be properly evaluated.

Accompanying the pain, the patient may develop *nausea* and occasionally *vomiting*. A feeling of faintness is not uncommon. As the urgent symptoms subside, symptoms and findings associated with peritoneal hemorrhage manifest themselves. The pulse rate increases as the volume decreases. The patient develops a progressively more marked pallor, particularly manifest in the mucous membranes. The blood pressure may begin to decline. Serious blood loss results in the picture of shock.

The loss of blood may be very moderate in some cases of tubal abortion so that a *hematoma* slowly accumulates in the pelvis. These pelvic hematoceles may become walled off and remain for weeks and months. The patient will continue to have pain in the lower abdomen and pelvis, a sense of discomfort on moving, and perhaps a persistence of the vaginal bleeding. Recurring attacks of pelvic pain or continued discomfort usually necessitates surgical intervention.

**Diagnosis.**—The diagnosis of ectopic pregnancy must usually be made by *vaginal examination* of the pelvic organs after a review of the *patient's history*. Pelvic inflammatory disease or an intentional abortion very often predisposes to the development of an ectopic gestation. Investigations to determine the patency of the reproductive tract in the study of sterility may establish a patent tract in an abnormal fallopian tube and make possible a tubal pregnancy. The enlarged tube

is usually palpated as an exceedingly tender adnexa. The pregnant tube, its serosal covering, and the adjacent peritoneum all convey a localized tender area. Usually the pregnant tube is anterior, but it may be prolapsed behind the uterus. Movement of the uterus away from the involved side elicits pain. The opposite adnexa is usually normal to palpation, but it may be grossly enlarged as a result of a pelvic inflammation which so often predisposes to ectopic gestation. If the duration of symptoms is over an extended period, a doughy hematocele may be palpable or a large mass adjacent to the uterus with indefinite land marks may be outlined. If there is difficulty in establishing a diagnosis, a few days' observation of the patient will usually produce some change or findings which will confirm the impression.

The *hormonal tests* for pregnancy may or may not yield important information. If the test is positive, it is indicative only that a pregnancy is present, not necessarily in the tube. In the event that the test is negative, an ectopic pregnancy is not ruled out. The test will become negative five or six days after the chorionic vesicle has largely separated from the tubal wall. Puncture of the cul-de-sac with a large needle is a harmless procedure and, when old blood is obtained, it is of significance in establishing the presence of bleeding into the peritoneal cavity. Some surgeons who have developed marked dexterity in pelvic surgery through the vagina prefer to open the cul-de-sac and explore the peritoneal cavity. This procedure may be difficult for most physicians and so it is not recommended.

**Treatment.**—The treatment of ectopic pregnancy is *surgical*. The involved tube should be removed with as little manipulation of the environmental viscera as possible. At times the adjacent ovary is so intimately a part of the tube that it must be sacrificed for expediency. The patient who enters the hospital in shock from marked loss of blood should have a liberal *blood transfusion* as soon as possible. Usually it is well to begin the transfusion and the operation at the same time. It may be necessary to give several transfusions in an attempt to replace adequately a serious loss of blood. *Parenteral fluids* are essential and should largely be administered subcutaneously; however, only blood will replace the necessary hemoglobin that has been lost from the circulation. Prompt and liberal blood transfusions have done as much for the improved therapy of conditions associated with marked hemorrhage as any other point in their therapy.

## THREATENED ABORTION

A threatened or inevitable abortion may produce pelvic pain. This pain is colicky and simulates dysmenorrhea or mild labor pain. The intermittent character of the pain is typical, and the pain is confined to the lower abdomen or pelvis. Vaginal bleeding is usually present and is variable in amount. There may be simply spotting, or the patient may bleed profusely. The external blood loss is always an indication of the amount of blood the circulation has lost, for there is little concealed bleeding.

In the *diagnosis*, the history of a period of amenorrhea is important. Nausea with or without vomiting may have been present. The signs and symptoms of early gestation can be elicited. Pelvic examination should reveal a uterus proportionately enlarged to the period of amenorrhea, and softened. The adnexa are normal and freely movable.

## NEOPLASMS

**Mechanisms by Which Pain is Produced.**—*Pain may not be a prominent symptom* in neoplasms of the reproductive organs, but discomfort of one type or another often brings the patient to a physician. A tumor of the ovary or of the uterus may grow to unusual proportions without discomfort to the patient. It may manifest its presence in several ways: In the first place, its environment may be such as to produce pain. A small growth separating the leaves of the broad ligament will be painful, for these peritoneal folds are richly supplied with nerves. A tumor in the region of the bladder will result in discomfort and urinary symptoms at an early stage because it will interfere with the proper functioning of this organ. In the same way, a growth in the posterior cul-de-sac may compromise the lumen of the rectum and cause pain and constipation. A tumor which fills the pelvis may produce pressure symptoms on the environmental organs, a sense of weight in the pelvis. If the tumor rises above the brim of the pelvis and grows free in the abdominal cavity, it can continue to go unnoticed. Discomfort produced by a neoplasm is largely dependent on its *location*.

A tumor or cyst can produce pain if it is *pedunculated*, so that torsion of the pedicle can take place. The pedicle may be part of the tumor or its environment. An ovarian tumor may produce torsion of the entire adnexa, thereby causing changes in the tube and ovary. Such *rotations* produce pain by tension and stretching of the peritoneal covering, by the

necrobiotic changes induced in the tissues because of interference with the normal blood supply, and by peritoneal irritation.

Neoplasms can produce pain by *necrotic changes* that take place within them. A *fibromyoma* of the uterus may be symptomless for years, and suddenly it produces abdominal pain and becomes tender to palpation. In most instances these degenerative changes are the result of a change in the blood supply to the tumor, but they may be due to rapid growth and stretching of overlying serosal surfaces. Rarely, the occurrence of pain in a benign neoplasm may herald malignant change.

Tumors and cysts of the reproductive organs may cause pain as a result of *adhesions* to environmental viscera. These adhesive bands interfere with the free movement of abdominal structures and with normal peristaltic action of the gastrointestinal tract. These abnormal unions produce traction on structures and their peritoneal relationships, so that a variety of aches and pains may ensue. They may likewise interfere with the normal function of an organ with its resultant discomfort.

Lastly, neoplasms may produce pain by a *direct infiltration* of contiguous tissues and the involvement of nerve trunks. Carcinoma of the cervix produces pain by an invasion of the tissues about the cervix and by the concomitant inflammation which usually exists. The cervix becomes fixed in its environment and painful to movement. Direct nerve involvement occurs when the bases of the parametria become involved. This pain increases in severity with the progress of the disease.

**Ovarian Neoplasms.**—Ovarian neoplasms do not often produce pain if they grow freely in the pelvis or abdomen and do not compromise adjacent structures. When these ovarian tumors fill the pelvic cavity, they may cause a sense of weight or pressure in this region. *Small solid* ovarian neoplasms may be associated with a heavy uncomfortable feeling in one side of the pelvis. If an ovarian cyst or tumor becomes *adherent* to omentum or intestine, fleeting pains or a sense of discomfort may result. Exercise and sudden movements may bring on attacks of pain. Urinary difficulties will arise if the tumor is in the *anterior portion* of the pelvis and exerts pressure on the bladder, interfering with its complete filling and emptying. *Dermoid cysts* of the ovary are likely to remain in the anterior quadrants of the pelvis. Similarly, a tumor in the hollow of the sacrum may interfere with the normal emptying of the bowel.

Tumors in this region may lead to chronic backache. *Malignant tumors* are often associated with ascites, so that pressure symptoms may arise from the increasing abdominal distention. *Implantation metastases* involving any of the abdominal organs may produce pain referable to the organ involved.

*Torsion of the pedicle* of an ovarian neoplasm results in the development of an acute abdominal condition. If the twist is complete, the pain is sudden in onset, sharp, lancinating, and is usually referred to the pedicle. This initial discomfort is probably ascribed to peritoneal tension, stretching and trauma. Necrobiotic changes begin in the tumor as a result of the interference with the blood supply and result in hemorrhage, thrombosis and necrosis. The tumor becomes very tender and usually increases in size. Peritoneal irritation is produced by these changes in growth and the acute symptoms are largely the result of the peritonitis. The subsequent course may vary. The peritonitis may extend to involve the general peritoneal cavity if the condition goes unrecognized. Rarely, an ovarian tumor may become completely severed from its pedicle and acquire a secondary attachment and blood supply.

The *diagnosis* of ovarian cysts and tumors depends largely on pelvic examination. The presence of ascites in association with an ovarian new growth is strong evidence of its malignant character. x-Ray examination of dermoid cysts may reveal calculous deposits and thereby reveal their true character.

*Treatment.*—All ovarian neoplasms should be removed surgically. The small cysts frequently found in ovaries are the result of normal ovarian activity and need not be disturbed. These are the follicle cysts, the lutein cysts, and the follicle hematomas. They will undergo spontaneous retrogression. Simple ovarian cysts can be removed without disturbing the remaining pelvic organs. If the neoplasms are bilateral, if they appear malignant or questionably so, it is advisable to remove both adnexa and the uterus supracervically. Ovarian neoplasms at the menopause and in the postmenopausal period should likewise be treated in this manner. Radiation should follow the removal of malignant ovarian neoplasms to improve the prognosis for the patient.

*Fibromyomata of Uterus.*—Fibromyomata of the uterus rarely produce pain for they are devoid of any nerve supply. They may grow over a period of years without any serious interference to the patient. Many women are seen by a physician for the first time for some other than a pelvic complaint and they are shocked to learn that they have been



harboring huge fibroid tumors. These interesting neoplasms produce discomfort by interfering with environmental structures, by undergoing necrotic changes, and by producing adhesions.

A sense of *weight* or *heaviness* in the pelvic regions is the most common complaint. A myomatous uterus restricted by the pelvic girdle will produce pressure symptoms, while one riding above the brim of the pelvis may not inconvenience the patient in any way. Tumors in the hollow of the sacrum produce chronic low back pain. Intraligamentous growths produce a constant ache in the side involved, occasionally punctuated with sharp stabs of pain. Even small tumors in the region of the bladder soon cause frequency and later dysuria.

The *development of pain* in a symptomless fibromyoma is always an ominous sign. The tumor itself may become tender on palpation, usually increasing in size at the same time. This local tenderness and discomfort is indicative of *degenerative* changes within the tumor nodule as a result of an altered blood supply. Pain or discomfort in an environmental viscus may mean an increase in the size of the tumor as a result of rapid growth or changed relationships within the pelvis. The pain may be in the form of an acquired dysmenorrhea. Usually such painful menstruation develops in the presence of an adenomyoma or a complicating endometriosis of the adnexa. Endometrial implants or a chocolate cyst of the ovary are not infrequent complications of fibromyomata of the uterus. A submucous tumor may gradually become extruded into the uterine cavity and develop polypoid characteristics. Such tumors may be completely extruded through the cervical canal and into the vagina. Cramplike pain, often colicky in character and simulating uterine colic or labor pains, may persist for days and weeks. Thus, discomfort may be severe enough to require sedation. Bleeding over a prolonged period of time may exsanguinate the patient.

*Extensive necrosis* in a tumor may be associated with *infection*, producing severe localized pain. Abdominal tenderness and rigidity may develop simulating acute appendicitis. The tumor may increase in size rapidly and may involve the adjacent peritoneum. Progressive involvement of the peritoneal cavity may occur if appropriate treatment is not instituted. The following history illustrates some of the difficulties which may arise in establishing a diagnosis of *acute degeneration of a myoma complicating a pregnancy*:

*Case III.*—Mrs. R. W., aged twenty-five, Unit No. 239142. This patient was admitted on the Chicago Lying-in Hospital on July 3, 1940. She had been under observation in the Prenatal Clinic for a normal gestation of approximately five months' duration. Pelvic examination earlier in pregnancy had revealed a normal uterus enlarged to the size of a three months' gestation. On the evening of June 18, 1940, she suddenly developed pain in the lower abdomen. This was cramplike in character. It persisted throughout the night and progressively became more severe. The next morning the pain was generalized throughout the abdomen and necessitated an opiate for relief. There was no vomiting or other symptoms of interest.

The patient appeared acutely ill; she was lying on her back with her right leg flexed and she moaned continually. The abdomen appeared to be enlarged to the size of a twenty weeks' gestation, but the uterus could not be outlined. Generalized tenderness could be elicited and this was most marked over the right lower quadrant. Pelvic examination revealed little additional information, for the splinting of the abdomen made it impossible to palpate the uterus with any degree of accuracy. The following were the laboratory findings: hemoglobin, 10 gm.; cell volume, 32 per cent; W.B.C., 11,000.

The patient had been told that she had chronic appendicitis and this fact had to be considered in the differential diagnosis. Examination under anesthesia made it possible to palpate the uterus and a myomatous nodule 5 or 6 cm. in diameter could be palpated in the right lower quadrant. At laparotomy, the acute degeneration of this tumor was evident. The necrobiotic changes had already induced a localized peritonitis.

The *treatment* of fibromyomata of the uterus depends on many factors; the size of the tumor, the presence of symptoms referable to the tumor, the age of the patient, and the location of the tumor. Many women harbor small symptomless myomata for many years without discomfort or trouble of any kind. These innocuous tumors need not be treated. It is well, however, to keep such patients under observation. Treatment is indicated if the tumor suddenly increases in size, if it becomes tender, if it produces pressure on adjacent organs, or if it causes marked changes in the menses. Large myomas, tumors which produce discomfort because of their size or location, tumors that are associated with prolongation of the menstrual flow, with an increase in the amount of the flow, or with irregular bleeding, should be removed. One should be less conservative at the menopausal period for the reproductive organs are no longer essential for the welfare of the patient. *Young women* who are desirous of offspring should be carefully observed and the neoplasms treated only in the event it is no longer safe to leave them.

*Surgery* is the treatment of choice. It is usually necessary to remove the uterus and its tumors supravaginally. The adnexa should be left in women prior to the menopause unless the tubes and ovaries are abnormal. In the menopausal period and thereafter, the adnexa should be removed with the uterus.

If the cervix is deeply lacerated or diseased, the uterus can be removed completely. Radiation by means of x-rays or radium is less popular than formerly. This method of treatment is reserved for women who are poor surgical risks and near the menopausal or who are in the postmenopausal period, when ovarian function need no longer be conserved. The tumors must be small and interstitial in location. There must be no complicating pathology. Usually 3000 mg. hours of radium will suffice to bring on an artificial climacteric and produce atrophy of the neoplasms. The enucleation of tumors and the conservation of the uterus should be rarely carried out. It is a suitable procedure in a few women who have a single or several isolated tumor nodules and who are anxious to overcome sterility. The operation carries greater hazards than incomplete hysterectomy.

#### BACKACHE

Backache is one of the most common complaints in women and its cause is usually referred to the reproductive organs. Acquired *retrodisplacements of the uterus* will produce a lumbosacral backache, but the mere discovery of a malposition of the uterus does not conclude a complete examination into the cause of the low back discomfort. *Abnormalities of the pelvic girdle* and its intricate supporting structures are much more common causes of backache than retrodisplacements.

In the routine pelvic examination of young women, symptomless retroversions of the uterus are found frequently. This abnormal position of the uterus in these women has probably existed for years or even from birth. It is not likely to interfere with normal physiologic function of the reproductive organs. Acquired retrodisplacements most often follow childbirth. The weight of the uterus during the puerperium, the relaxation of the supporting structures and the trauma to the pelvic floor and the ligaments and fascias of the uterus all contribute to the malposition. Backache may develop for the first time in the postpartum period.

*Childbirth* is likely to produce backache of pelvic origin. The pelvic girdle is seriously interfered with during pregnancy and labor. The pelvic joints become more movable as a result of an increased separation of the pelvic bones. Pelvic supports become more supple because of the increased fluid and blood supply. The added load of the baby and the altered posture and gait provide increased stresses and strains on the keystone of the bony framework. Separation of the symphysis pubis

and changes in the sacro-iliac joints, and more rarely in the sacrococcygeal joint, are aggravated by long labors and difficult operative interventions. In most individuals, these pelvic changes rapidly disappear after delivery, but in many women residual changes remain to produce chronic low back pain.

*Chronic arthritis* involving the pelvic bones is a common cause of low back pain, particularly in middle-aged women. The early changes of arthritis may be difficult to demonstrate, but the progressive character of the pain usually makes the condition manifest. The disease usually involves the sacro-iliac joints, but it may involve other localities as well.

**Diagnosis and Treatment.**—The diagnosis of the cause of backache may be difficult and the successful treatment of this complaint even more trying. Backache due to *acquired retrodisplacements* of the uterus should be relieved when a properly fitted pessary brings the uterus anterior. Suitable exercises will aid in the restoration of the uterus to a normal position and its maintenance in this desirable state. Relief of the discomfort is ample proof that the malposition was responsible. In the first few months after childbirth, acquired retroversions can be successfully corrected by a proper pessary and exercises. However, retrodisplacements not associated with childbearing are not amenable to permanent cure. The organ will remain anterior as long as the pessary remains *in situ*, but it will usually return to its former position after the ring has been removed. It will herald its return to the former position by a return of the patient's backache. *Surgical correction* of the malposition is indicated if the backache is definitely of uterine origin, if the discomfort interferes seriously with the patient's welfare, and if it is not expedient to wear a pessary. Few uterine suspensions are indicated during childbearing years when the family is still incomplete. Operations for the correction of retrodisplacements were the most frequent gynecologic surgical procedures a decade or two ago but, today, they are becoming increasingly less common.

*Adherent retrodisplacements* are more difficult to evaluate as to diagnosis and treatment. Inflammatory conditions of the adnexa often result in adnexal masses which drag the body of the uterus posteriorly as they slowly retrogress. Ultimately, the uterus and its adnexa become firmly bound down in the hollow of the pelvic cavity. Discomfort in the lower abdomen and backache may seriously hamper the patient's normal activities. Endometriosis is the next most common cause of adherent retroversions. In this condition, endometrial im-

plants on the ovaries, the uterus and in the cul-de-sac produce a characteristic picture. The ovaries become enlarged by chocolate cyst formation. The adnexa and the uterus, together with the environmental viscera, become firmly bound down in the pelvis. The backache may not necessarily be due to the retroversion but to the extensive changes in the pelvic organs. An acquired dysmenorrhea as well as backache are common symptoms. *Conservative* management of these conditions is indicated until such time as the disability seriously interferes with the patient's life, after which it may be necessary to resort to surgery.

### DYSMENORRHEA

Pain at the time of the menses is such a common complaint that it has merited the distinction of a clinical entity. Nevertheless, like backache, it is a symptom rather than a clinical condition and as such is identified with many pelvic disorders. Dysmenorrhea may have had its origin at the time of the first menses, or it may be acquired later in life following childbirth or as a result of pelvic disease. The discomfort may be so mild that the patient is not seriously inconvenienced; on the other hand it may be so severe as to invalid the patient for several days each month, driving her to extreme ends to seek relief. In many instances the dysmenorrhea is gradually ameliorated and may completely disappear following reproduction. In other women the discomfort increases in severity until the patient can no longer carry on.

The *pain* associated with menstruation is usually cramp-like and colicky in character. In the presence of a retrodisplacement of the uterus it may be referred to the back. It may precede the onset of bleeding by several hours. Often the pain is ushered in by prodromal headache, nausea, with or without vomiting and vertigo. These prodromes may cause greater discomfort than the pain.

A careful *history* is an important step in the treatment of this troublesome condition. Psychogenic factors play an important part in the causation of dysmenorrhea. A pelvic examination is necessary to determine the normalcy of the reproductive organs. The treatment should then be directed to the relief of pain and the removal or correction of the underlying causes.

*Antispasmodic* and *analgesic drugs* have been used singly and in combinations. There are several new antispasmodic drugs which hold some promise of success. A useful remedy

employed at the Chicago Lying-in Hospital consists of the following:

℞	
Camphor monobromate .....	½ gr.
Atropine sulfate .....	1/500 gr.
Papaverine hydrochloride .....	¼ gr.
Phenacetin .....	3 gr.
Acetyl salicylic acid .....	3 gr.
One capsule can be taken every four hours.	

*Hormone therapy* is of value in selected cases. Estrogens are helpful in young women in whom a hypoplasia of the genitalia exists. The growth of the reproductive organs induced by this hormone may lead to a disappearance of the dysmenorrhea. Progestin may be of value in some cases.

Dysmenorrhea resulting from acquired disease, such as *infections, endometriosis or neoplasms*, can only be cured by treatment directed at these conditions. Radical surgery should not be attempted until such time as other factors have been corrected. Simple dilatation of the cervical canal may result in temporary, and occasionally in prolonged, relief. This may be due to the trauma to nerves in this region. Rarely is a resection of the presacral nerve indicated.



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### PAIN ARISING FROM LESIONS OF THE NERVES AND SPINAL CORD: DIFFERENTIAL DIAGNOSIS AND TREATMENT

THIS morning we are to discuss the subject of pain arising from lesions of the nerves and spinal cord. Certain varieties of pains we refer to as "*intractable*," meaning that they do not yield to adequate and specific treatment of the underlying pathologic condition. Among them may be mentioned the various neuralgias (trigeminal, glossopharyngeal, etc.), the pain of inoperable neoplastic disease involving nerve roots, "lightning pains" of tabes dorsalis, and so on. They must usually be alleviated by some method of interference somewhere along the conduction pathway by which the painful stimuli reach the level of consciousness in the cerebral cortex. Other forms of pain, however, are characteristic of certain definitely remediable pathologic conditions, some examples of which I wish to show you today:

#### PAIN ARISING FROM AN EXTRAMEDULLARY, INTRADURAL SPINAL TUMOR

*Case 1.*—This forty-eight-year-old married woman noticed pain as the initial symptom of her present illness. About two years ago she began to have a feeling of soreness encircling the lower part of the thorax on the left side below the left breast. This soreness was not constantly present, but it bothered her a good deal of the time and was considered by her to be a form of "pleurisy" or rheumatism. On direct questioning, however, the patient stated that she also noticed that in coughing or sneezing, a pain would radiate in girdle fashion around from the spine toward the sternum, but since it was very transitory, she paid no attention to this. This pain continued to exist without change until about six weeks ago, when the patient began to notice some tingling in the toes of her right foot. Within a few days there was a definite feeling of paresthesia extending up the right leg and the tingling feeling began in the left foot. At about this same time the patient also began to notice some stiffness and apparent weakness in the left leg, so that she favored it somewhat in walking. About ten days ago the patient entered another hospital with these



complaints and a spinal puncture was performed. Within twenty-four hours after this puncture, the paresthesia of which the patient had complained rose bilaterally up both extremities and the lower part of the trunk and reached the level of the old "neuralgic" pain which had been present for two years. In addition to this, the patient became weak in both legs and began to have some difficulty in voiding.

The patient was then transferred to this hospital and the report on her spinal fluid was sent along; this showed a cell count of 2 and normal serologic findings, but the total protein was 250 mg. A diagnosis of probable extramedullary spinal cord tumor was made and the level was assumed to be the eighth dorsal segment, which lies approximately beneath the sixth dorsal vertebra. *x*-Rays of the thoracic spine yielded further confirmatory evidence of this, for the pedicles of the fifth and sixth dorsal vertebrae were thinned and widened.

The patient was accordingly operated upon four days ago and a hazelnut-sized extramedullary meningioma was found which was inside the dura and attached to the posterior root of the eighth dorsal segment of the cord. The postoperative course was smooth and the patient has already noticed a marked improvement in motor, sensory and sphincter functions.

Intercostal girdle pain like that described by this patient is very significant, particularly when the pain is enhanced by *coughing* or *sneezing*. It very often is of early significance in benign spinal cord tumors and, if recognized, may obviate allowing the condition to progress to the point of permanent damage to the spinal cord. The reason the pain is enhanced by coughing and the like is that, when small, the tumor still floats, more or less, in the fluid surrounding the cord. When coughing produces venostasis in the brain and distends it, thereby squeezing fluid down into the dural sheath of the cord, the floating tumor tugs at the posterior root to which it is attached and produces the pain.

#### TABETIC RADICULITIS

*Case II.*—This thirty-eight-year-old divorced office worker gives a history of having had a syphilitic infection which she states was the cause of the dissolution of her marriage. She has received adequate therapy at competent hands and her blood and spinal fluid serology has been completely normal for several years. For two and one-half years, however, the patient has suffered from a severe and almost constant pain in the region supplied by the spinal root of the tenth dorsal segment of the spinal cord—in other words, a girdle pain running around the trunk toward the region of the umbilicus on the right side. This pain is nearly constant except that it is worse at night than in the daytime, and according to the patient it resembles a severe persistent neuralgia. Coughing or straining does not change the character of the pain and also, unlike the previous case, the patient notices tenderness to light touch over the skin area involved. On further questioning the patient states that this pain in its initial stages appeared in violent paroxysms which would last from several minutes to half an hour. Once or twice there was some associated nausea, but both this feature and the paroxysmal character of the pain have now disappeared.

This type of root pain is characteristic of the *radiculitis* and *ganglionitis* one sometimes sees in tabes. Whereas this patient has none of the cord changes one observes in tabes, except that her knee jerks are markedly diminished bilaterally, she nevertheless has the "lightning pain" feature of this condition.

The patient was accordingly operated upon a couple of weeks ago under local anesthesia, and the specific posterior root involved was identified by picking it up in forceps and checking the area of pain with the conscious patient. The root was then clipped and divided proximal to the dorsal root ganglion—in other words, between it and the spinal cord—and in order to make perfectly sure that the correct root had been divided, the contiguous roots above and below were also treated similarly.

Since the time of operation this patient has had none of her previous tabetic root pain and neurologic examination has demonstrated a band of anesthesia about an inch in width in the region of the tenth dorsal segment of the cord. Both above and below this area of anesthesia there is a narrow strip of hypesthesia, possibly half an inch in width. This finding of minimal sensory loss, of course, confirms the well known fact that there is a good deal of overlapping of the sensory dermatomes.

#### POSTHERPETIC NEURITIS

The next case also demonstrates root pain like that in Case II except that the etiology is different.

*Case III.*—This patient is a fifty-four-year-old man who, fifteen years ago, had a rather marked herpes over the sixth dorsal dermatome on the right. This herpes and its associated eruption cleared up after several months, but for years afterward this skin area was slightly hypersensitive. Two years ago the patient, after having worked very hard and being somewhat rundown physically, had another severe attack of herpes in the same region for which it was necessary to hospitalize him and give him sedation. The acute attack lasted about three months but, following it, the patient had a painful and disabling hypersensitiveness in the old herpetic area. The pressure of bed clothes or of his underwear was almost intolerable to him and for some time he tried various remedies such as diathermy, mud baths, massage, etc.

About a year ago this patient came to us and was given deep x-ray therapy over the involved roots in the region of the fourth dorsal vertebra. This resulted in some improvement and, a few months later, another course of similar therapy was given. This, however, did not help the patient sufficiently so that he felt at all comfortable and he therefore

entered the hospital rather desperate to have radical measures taken. Since his general condition was good, it was felt that a posterior root section was justifiable and one was accordingly performed, the two contiguous roots being severed as in the preceding case. The patient has had no difficulty since.

#### PERIPHERAL AVITAMINOTIC NEURITIS

The following case illustrates the way in which extreme pain may occur spontaneously in the peripheral nerves:

*Case IV.*—This young man is a thirty-four-year-old salesman who was sent in from an out-of-town clinic with a tentative diagnosis of some paralytic condition, possibly multiple sclerosis. No further information was available at the time until the patient was brought into the Out-patient Department. When seen he lay on a stretcher with his knees doubled up and he was obviously extremely emaciated and gravely ill. When any effort was made to touch him or move him or straighten out his legs, he literally screamed with pain. He was therefore admitted to the hospital and given sedatives in sufficient degree so that a reasonable neurologic examination could be made. It was then found that the chief objective finding, in addition to the emaciation and the extreme sensitiveness of all the muscles, particularly in the extremities, was that the deep reflexes in both upper and lower extremities were absent. There was no sphincter difficulty and, while the patient stated that he had some paresthesias in the hands and feet, no objective sensory loss could be determined here.

On going into this patient's history, it was found that he had been a chronic alcoholic for several years. Previously he had not been successful with anything and had not worked steadily at any occupation during his adult life. Two years previously he had married a widow who had four children and she had been forced to support the patient in addition to her children, thereby securing for him the opprobrium of all of the relatives in both his own and his wife's family. The patient, being a sensitive soul, took more and more to drinking and less and less to eating properly, and, indeed, had been subsisting for several months on virtually nothing but an occasional meat sandwich in addition to his alcohol.

It was obvious that this man suffered from an alcoholic peripheral neuritis enhanced by an avitaminosis. He was immediately given the proper amount of fluids, put on a high caloric diet, and was given high concentrations of vitamin complexes. Within a week most of the pain had disappeared, and within a month he was able to walk about on the ward. He remained in the hospital, however, for two months more, during which time he gained 20 pounds. He was then discharged perfectly well, so far as could be determined, except that his deep reflexes were still absent. Reports from him one year after discharge from the hospital indicate that he is doing heavy manual labor on a Michigan farm, is not drinking, and is feeling better than he ever had in his life.

## PAIN ARISING FROM A PERIPHERAL NEUROFIBROMA

This case illustrates a point in the examination of a patient which we all know but occasionally neglect or overlook:

*Case V.*—The patient is a sixty-year-old executive who for many years has noticed sensitiveness over the anteromedial aspect of the proximal portion of the right thigh, in the distribution of the anterior crural nerve. The "neuralgia" and hypersensitiveness in this area has varied considerably from year to year and from season to season. The patient, however, has not connected it with any particular time of the year, nor with any related observations concerning the state of his general health. Being financially affluent, he has sought and received considerable expert medical opinion regarding this discomfort and the usual diagnosis has been *meralgia paraesthetica*.

Examination revealed absolutely nothing. The trophic supply to the skin area about which the patient complained seemed perfectly normal, there was no pigmentation, sensation to all modalities was normal, and there was no evidence of any muscular nerve being involved and resulting in muscular atrophy. The patient, however, had lost patience with his complaint and the anterior crural nerve was therefore dissected surgically. In the region of the inguinal ligament, a small neuroma about split-pea size in portions was discovered and extirpated. This operation was performed about a year ago and the patient has been completely free of pain since and does not object to the anterior crural anesthesia which was produced.

This case should remind everyone that, when examining a patient who has pain of apparent nerve origin, the presence of a lesion involving the *distal* portion of the nerve itself should always be considered. While not at all common, it is an experience that almost all neurologists and neurologic surgeons have of finding a patient with symptoms of chronic sciatica or chronic ulnar neuritis, etc., who has a neuroma which can be palpated along the course of the nerve. Such neuromas are sometimes part of von Recklinghausen's disease and a few skin tumors or *café au lait* skin pigmentations can be discovered by complete examination.

## NEURITIS RESULTING FROM FOCAL INFECTION

*Case VI.*—This patient is a forty-four-year-old woman who, eighteen months ago, became very uncomfortable with indefinite neuralgic pains around the right shoulder and upper arm. The skin in this area was sensitive and sleep was interfered with because of the sensitiveness, which seemed to increase at night. The patient had two attacks of coryza, occurring about six weeks apart, and the pain was considerably increased during both of them. She has also noticed that inclement weather caused an exacerbation of her discomfort.

After about six months of the above complaints, the patient placed herself in the hands of an internist who went over her

completely from the standpoint of possible foci of infection. The most definite ones he could find were two rather large apical abscesses, one at the root of the right lateral incisor of the lower jaw and the other at the root of the left third molar in the upper jaw. He advised that the molar be extracted and the incisor be treated by drilling out of the root canal and filling of it after sterilization of the abscess cavity. This was done and the patient has been free of her "neuralgia" for nearly a year.

### CERVICAL RIB

*Case VII.*—This young woman is a graduate nurse who first began to notice pain at about the age of eighteen. This pain was very indefinite at first and seemed chiefly to indicate a stiffness in the muscles of the neck, so that she was uncomfortable at night unless she used a particularly soft pillow which her mother had made for her especially. This pain was enhanced by heavy lifting but at no time was disabling.

At about the age of twenty-five, the patient, while nursing some partially paralyzed individuals, had to do a great deal of heavy lifting in order to turn them. This made the pain in her neck quite acute, so that any sudden motion or twisting was painful; in addition, there was a radiation of pain with some slight paresthesia down the ulnar distribution of the left arm.

Examination failed to reveal anything objective from a neurologic standpoint. There was no atrophy or any trophic or sensory disturbance in the skin, and the general neurologic examination was normal. On asking the patient to raise her left arm above her head, however, it was noticed that the pulse was considerably diminished in volume. Palpation in the antero-inferior triangle of the neck on the left side revealed a bony protuberance which felt as though it were almost beneath the skin.  $x$ -Ray examination of the neck showed a cervical rib on the left side more than 2 inches in length.

This patient was operated upon by a well known thoracic surgeon who, via a posterior approach alongside the scapula, removed the rib in its entirety. This operation, while complete, is a difficult and rather specialized one and it may be noted that even in this expert surgeon's hands, there was a slight pleural tear and consequent slight temporary collapse of the lung. The majority of these patients can be completely relieved merely by dividing the anterior scalene muscle, which has a tendency, when intact, to press the brachial plexus against the cervical rib. When the scalene muscle is divided, the plexus falls away sufficiently to free it and relieve all symptoms. Cervical rib is a congenital condition which occurs most frequently in females and most often on the left side. It usually produces symptoms which reach surgical proportions at the age of skeletal maturity, *i.e.*, at about the age of twenty-five.

## PROTRUDED INTERVERTEBRAL DISK

The next and last case illustrates a condition to which much attention has been directed in the last several years:

*Case VIII.*—The patient, a forty-year-old laborer, first noticed his disability one year ago while working as a packing clerk in a factory. It was his job to lift heavy pieces of machinery and place them in crates on loading platforms. This required several score such exertions in the course of a day, the weights averaging around 100 pounds or more; it also involved twisting at an angle of about 90 degrees as he deposited each piece of machinery in its crate. One morning when coming to work on a rather cold day, when the patient felt rather stiff and not in first-class physical condition, he began to perform this kind of work immediately upon arrival rather than an hour or two later when he had become warmed up and limbered up. On picking up the first piece of machinery and twisting to the right with it, he noticed a sharp pain in the lower lumbar region which seemed to radiate part way down the back of the right thigh. This pain was exquisite and the patient did no more lifting that day, finally going home early because of his discomfort. He stayed at home in bed for three days in great discomfort, applying hot water bottles, etc. The pain then gradually began to leave him and, within a few more days, he was able to return to his work. However, on the first day of his return he again had an exactly similar experience, the pain again striking suddenly and fiercely in the lower lumbar region and radiating down the back of the right thigh. The patient was again forced to quit work, and this time, his company arranged for hospitalization and physiotherapy.

The latter went on for about a month, after which the condition had become considerably less painful but had resolved itself into what amounted to a chronic sciatica. There was at all times a rather dull annoying pain in the lower lumbar spine which was aggravated by certain motions, and a fair share of the time there was a radiation of pain down the back of the thigh to the lower part of the leg, which occasionally went as far as the heel. The patient, however, was able to walk, although he limped slightly, and he finally returned to work but was given a job which did not require lifting. In the meanwhile the physiotherapy went on, but there had been no improvement for several months at the time the patient was seen by us.

Examination showed a well built, muscular man of about forty. There was no pain over either sacro-iliac joint and very little on direct pressure over the lumbar laminae. The sciatic nerve did not seem tender on pressure. However, in raising the right leg in extension, the patient complained greatly of pain running down along the entire sciatic distribution. The patient's knee jerks were equal, but the right ankle jerk was considerably diminished compared to the left. The skin over the lateral part of the dorsum of the right foot seemed slightly less sensitive to pin prick and light touch than the similar area on the left foot. x-Ray examination of the spine revealed that the space between the fourth and fifth lumbar vertebrae was considerably narrowed.

In view of the above history of injury beginning this patient's complaints and the positive findings of diminished ankle jerk and narrow intervertebral space, a diagnosis of protruded intervertebral disk between the fourth and fifth lumbar vertebrae was made. It was felt that there was sufficient evidence to make such a diagnosis without injecting such material as

air or lipiodol in order to obtain myelograms, and it was even felt that lumbar puncture might not have been necessary, though one was done and the findings were normal. A hemilaminectomy of the right half of the laminae of the fourth and fifth lumbar vertebrae was performed, exposing the dura of the cauda equina, to the side of which a small grayish nubbin of tissue protruded. On palpating this material with a pair of tissue forceps, it felt rather rubbery in consistency. It was grasped with a small hemostat and very moderate traction was all that was necessary for a piece of material, half-moon shaped and about half the size of the terminal phalanx of the little finger, to be extracted. The wound was closed and from the day of the operation the patient has had no further complaints of the chronic pain which had previously incapacitated him for nearly a year.

#### COMMENT AND SUMMARY

All of the foregoing eight cases are fairly typical examples of specific types of pain arising from lesions affecting the nerves rather than the spinal cord. They have illustrated, respectively, pain arising from extramedullary intradural spinal tumor, tabetic radiculitis, postherpetic neuritis, peripheral avitaminotic neuritis, peripheral neurofibroma, neuritis resulting from focal infection, cervical rib, and protruded intervertebral disk.

You, of course, know that the cord itself, like the brain, does not become painful when afflicted by growths or other lesions, since there are no end organs for pain indigenous to it. Spinal cord tumors and epidural abscesses in the spinal canal, as well as fractures of the spine, etc., often produce local pain where they exist, but this is due to local pressure or erosion, or to irritation of the posterior roots in the neighborhood. Any of you who have seen a deliberate section of the antero-lateral tracts of the spinal cord performed on a patient under local anesthesia, will know it does not even produce pain to traumatize or divide intrinsic spinal cord tissue.

The important thing to remember about the above cases is the *selectivity* and *anatomic distribution* of the pain which the various types of pathologic conditions produce. Nerve pain is unlike that which occurs in visceral diseases, bone lesions, etc., in that the pain in these latter conditions is diffuse and does not involve definite dermatomes. If these facts are borne in mind and the lessons taught by these cases remembered, there should be no difficulty in the average practitioner making an accurate diagnosis.

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### PAIN IN MUSCLES, BONES AND JOINTS

PAIN is said to be a symptom, an entity of a subjective nature, which cannot be evaluated; and since it cannot be evaluated, it is often neglected. Leriche<sup>1</sup> originally felt that pain was a disease of the sympathetic nervous system, but more recently he writes that it is a "state of the mind" and concludes that we are becoming more sensitive to pain. Consequently pain should be accorded a greater role in our armamentarium of treatment. This clinic will illustrate some types of pain such as are seen in an orthopedic practice. Destructive lesions as a cause of pain are beyond the scope of this paper.

I believe that every pain has some meaning, no matter how neurotic a patient may be. It may signify only a slight or temporary physical or physiologic imbalance which nature was able to correct, and consequently from which no permanent pathologic state developed. Rigid flatfoot, osteoarthritis and malum coxae senilis are good examples of the end result of pains in childhood which were allowed to pursue their courses unheeded. Too many times they are called "growing pains," "rheumatism," or some other condition that will be outgrown. In infants, they are passed off as "teething pains." In a certain parish in Louisiana, infantile paralysis was known as "teething disease." Abels<sup>2</sup> has shown that fevers hasten teething; further than this he found no other relationship. He attributes many of the "growing pains" to a low vitamin diet. Even in adults some muscle and joint pains disappear on increasing the calcium or vitamin intake.

#### EPIPHYSEAL SEPARATION

*Case I.*—A boy, aged eleven years, was brought to his family physician for a pain in the right thigh in February and again in April. The diagnosis was rheumatism. Finally the pain became worse and necessitated occasional bed rest for three or four days. In the latter part of June the boy went to a scout camp. One day, while standing on his right leg and leaning against the door, another boy gave him a push which caused him to fall to the floor with



a rotating motion. This trauma precipitated an acute pain in the hip region. The boy was put to bed for a few days and was then taken home on a stretcher.

When seen in consultation, the patient was lying in bed with his right leg in outward rotation and in 15 degrees of adduction. By this time the acuteness of the condition had subsided so that he could shift his position without causing much pain. He was tall and slender and weighed about 100 pounds. There was a slight fullness over the hip region anteriorly; the thigh could be flexed about 30 degrees, adducted to from 5 to 10 degrees, but there was no

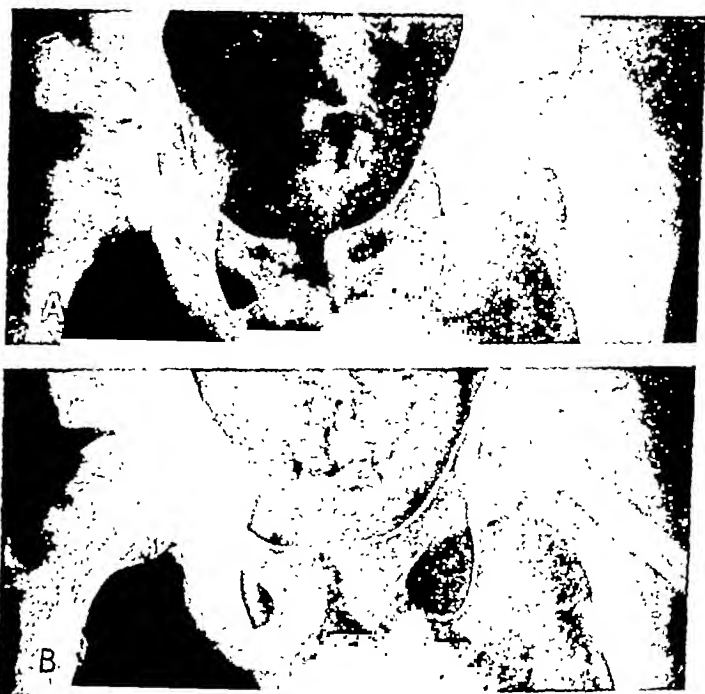


Fig. 1.—A, Femoral head slipped off the neck of the femur at the epiphyseal line. B, One year after reduction and insertion of a graft.

abduction or inward rotation. An x-Ray (Fig. 1) showed the femoral head had slipped off the neck of the femur at the epiphyseal line.

Suppose we have a patient who has suffered from a few days of discomfort in the thigh or hip region (which later increases in intensity) without any cause or perhaps only from minor trauma such as the stubbing of a toe. If this discomfort is followed by relief after a few days in bed and yet recurs from time to time in a child, say, between the ages of ten and sixteen, one should suspect an *epiphyseal separation*. An x-ray should then be taken of both hips.

If the process is just beginning, and is in the stage of pain relieved by a few days of rest and the patient has a slight limp with no limitation of motion, the x-ray may show a widening of the epiphyseal line and a diminution of the offset of the head with the neck, the disappearance of the so-called "epiphyseal hump." After the symptoms and signs become as advanced as in the foregoing case, one sees variable degrees of displacement of the head on the neck.

**Perthes' Disease, Tuberculosis, and Epiphysitis.**—Perthes' disease, tuberculosis and transient epiphysitis<sup>b</sup> come into the differential diagnosis. Also to be considered is whether or not the pathology is in the hip or knee. The pain in the thigh is often closer to the knee than to the hip. Many leg and thigh casts are applied under the misapprehension that the pathology is in the knee, even though an x-ray of the knee is negative.

*Perthes' disease* occurs in younger individuals, four to eleven years of age. The limp is painless. x-Rays show a flattened, fragmented head in normal relation to the neck.

*Tuberculosis* also begins at an earlier age and is accompanied by general malaise associated with more muscle spasm; the x-ray shows a destructive lesion on one or the other sides of the epiphyseal plate, more frequently on the shaft side with the head in good position.

*Acute transient epiphysitis* has its highest incidence before ten years of age. Symptoms localize rather promptly in the hip. Physical examination shows a slight fullness and muscle spasm with limitation of motion and flexion deformity. A fever (100–101° F.) is also present.

**Treatment of Epiphyseal Separation.**—The treatment of an epiphyseal separation with little or no displacement is to prevent weight-bearing and other stresses and strains until the epiphysis is fused. This treatment prevents further displacement. Treatment consists of *bed rest* or a *hip spica cast*, or a combination of the two. If there is an associated internal glandular disturbance, that should also be treated.

Elimination of *weight-bearing* need not be absolute for the entire period. Suppose a patient comes under one's care who is ten years of age; one would have some difficulty in keeping such a patient until he was sixteen if it were insisted that he wear a cast for the six years. Instead, the patient should be put to bed for four or five weeks or until the pain subsides and the hip feels free. Then apply a cast. After a variable period (four to ten months) you will note in the x-ray that the lines

of stress are becoming clearer and the epiphyseal line thinner. The patient is then ready to go without casts, but he must use crutches. Raise the heel of the shoe for the well leg an inch. This will make it easier to clear the floor with the affected leg and the patient will not be as likely to bear weight with this extremity.

In patients who are within two or three years of the end of the growing period, this course of treatment can be shortened to three or four months if a *drill*<sup>4</sup> is run through the shaft from the lateral surface, through the neck, and across the epiphyseal line into the head at several places. This should be done at the beginning of the treatment. In younger children, this is not to be recommended, as the premature fusion causes distortion of the head and neck of the femur.

Femoral heads that have slipped off should be *replaced*. If the head can be replaced without impairing its periosteal blood supply, a short period (one to two months) of bed rest should be instituted, followed by the cast and non-weight-bearing regimen, check being kept with x-rays. If the head does not maintain its density and contour, back to bed the patient must go. In Case I the patient was in a cast two months after being released from bed. If the periosteal blood supply is disturbed at the time of reposition, the patient will have to be in bed with traction as long as from fourteen to sixteen months. This is the only way to give a patient a round femoral head. Having severed the blood supply to the head, it undergoes death and softening. It then must be revascularized and recalcified. If weight is borne in this interval, the head will flatten. If this happens relatively early, the head is completely distorted. Surgical replacement is preferable to closed manipulation.

#### BURSITIS

When a patient presents himself with a pain that seems to be dependent upon joint movement, joint involvement is often erroneously suspected. One should develop the habit of thinking of each region in cross section and try to visualize each layer as a possible candidate for the pathologic site. For instance at the hip region, from within out there is the head of femur, ilium, hip joint capsule, some bursae, muscles and lymph glands which might be involved.

*Case II.*—A child about six years of age is referred for treatment of an acute tuberculosis of the hip. The history brings out the fact that the child has been running a temperature of 100° to 101° F. for three or four weeks and

that he has been complaining of a severe pain in the hip, especially on movement. Physical examination reveals a toxic appearing child, nothing unusual being noted until the right extremity is exposed. The child lies with this hip greatly flexed. When he lies on his back with the limb in extension, there is swelling over the hip joint region which extends upward under Poupart's ligament. This area is tender to palpation. Within a certain range of movement of the thigh there is no pain. If one attempts completely to extend or flex the thigh on the abdomen, the pain is increased. Buck's traction also increases the pain. There is a leukocyte count of 18,000. Urinalysis is negative, as is an x-ray of the bony structures of the hip region.

The outstanding features in this case are: (1) comfort with the hip in slight flexion; (2) swelling at the hip deep to the femoral vessels, which extends more proximally than the hip joint, and (3) pain on extremes of flexion and extension. Inflammation in the *iliopsoas bursa* will give this picture. The pain under these circumstances is due to compression of the inflamed bursa by pressure of the iliopsoas muscle when extending the thigh. When flexing the thigh, the iliopsoas tendon raises away from the bursa and consequently pulls on the wall of the bursa. This and the sign of increased pain in traction are valuable in ruling out an osseous lesion.

**TREATMENT.**—In a bursitis, the affected region should be immobilized in a position of comfort and the bursa should be aspirated. If the fluid is sterile, the condition will subside. If it contains organisms, the bursa should be drained as one would a septic joint. Failure to recognize septic bursae about a joint is responsible for many stiff and ankylosed joints, either because the bursa ruptured into the joint or the surgeon, failing to recognize the condition, cut through the infected bursa into a clean joint and thus infected the joint space.

#### CAUSALGIA

Do children develop causalgia? We are accustomed to associate causalgia with war wounds and other severe injuries. Leriche feels that causalgia occurs more frequently in civil practice than one would suspect.

**Case III.**—A healthy appearing girl about eight years of age presented herself because of pain in the right tibia. About four months previously she bumped the leg on her wagon but had no pain until two weeks later. The pain at first was periodic, lasting three or four days, and was acute enough to disturb her sleep. It was affected somewhat by play. Later the pain became continuous.

Physical examination was negative except for a tender area over the subcutaneous border of the right tibia in its middle third. There was questionable swelling but no redness or heat. The blood chemistry and serology were negative. An x-ray of the right tibia was negative. (An osteitis or periostitis should have caused enough reaction to be visible in the x-ray after this long

a time.) The left tibia showed a rarefied area near the upper metaphysis. The patient was getting a well balanced diet, and there seemed to be no home problems. Bed rest did not affect the complaint. Heat and massage made it worse. Pain along the shin is an early symptom in an arch strain; arch strain is relieved by rest; patients feeling best in the morning. Supportive shoes did not relieve the complaint. The foot posture was good.

**TREATMENT.**—Three injections of novocain and saline, each a week apart, relieved the patient of her pain. She has been under observation for one year.

#### FASCITIS (PAINFUL HEEL)

*Case IV.*—A middle-aged, heavy set woman presented herself with the complaint of pain in the heel of three months' duration which was getting worse. She has had supportive material in her shoes and much physiotherapy, without the slightest relief. Her condition was called an arthritis. There is



Fig. 2.—Introduction of needle from the medial aspect of the foot.

tenderness over the tuberosity of the os calcis at the origin of the plantar fascia. The sides of the os calcis are not tender. The x-ray shows a little lipping at the anterior end of the tuberosity.

I am inclined to call this a fascitis. Painful heels that are on a toxic or arthritic basis also present tenderness along the medial and lateral aspects of the os calcis. The lipping may or may not be responsible for the pain. Many feet show spurs in the x-ray but never give symptoms. Many painful heels do not get well with the removal of the spur.

**TREATMENT.**—The above patient has been well for two years after having received ten injections of saline and novocain. The needle is much more easily introduced from the medial aspect (Fig. 2) than through the sole of the foot; also a broader area can be covered through the one puncture.

## GOUT

*Case V.*—A young man, aged twenty-five, presented himself complaining of pain in the left heel of one year's duration. He had slipped on a step and had come down hard on this heel. It was quite painful in the morning and after sitting. His family physician had pronounced him in good health on several occasions. On examination, the origin of the plantar fascia and the

TABLE 1

PURINES ARE SUBSTANCES WHICH FORM URIC ACID\*

I	II	III
Foods That Contain a Large Amount of Purine	Foods That Contain a Moderate Amount of Purine	Foods That Contain No Purine
Sweetbreads	Chicken	Milk
Liver	Mutton	Eggs
Kidney	Bacon	Cheese
Squab	Oysters	Caviar
Calves' tongue	Herring	Shad roe
Turkey	Salmon	Nuts
Pork	Lobster	Gelatin
Veal	Crab	Sugar and sweets
Sausage	Whitefish	Coffee
Beef		Tea
Goose	Asparagus	Cocoa
Anchovies	Lima beans	Fats of all kinds
Sardines	Navy beans	Fruits of all kinds
Trout	Kidney beans	Cereals (except whole grain)
Pike	Kohlrabi	Bread (except whole grain)
Perch	Onions	Vegetable soup (made without meat)
Codfish	Peas	Vegetables of all kinds except:
Lentils	Spinach	Lentils
Gravies	Mushrooms	Spinach
Meat extractives	Oatmeal	Mushrooms
Meat soups	Whole grain cereals, such as cooked whole-wheat and wheat biscuits	Peas
	Whole grain bread, such as whole-wheat and graham bread	Lima beans
		Navy beans
		Kidney beans
		Kohlrabi
		Asparagus
		Onions

*Avoid the Following:*

Radishes, watercress, paprika, garlic, mustard, relishes, horse-radish, catsup and other spices and condiments.

Rich and indigestible foods and rich sauces and gravies.

Alcoholic beverages.

\* From a Mayo Clinic diet list according to their purine content. The patient chooses his foods from columns III, II and I according to the severity of his gout.

inner side of the os calcis were tender. The x-ray showed a small spur. Supportive shoes, daily diathermy and saline-novocain injections for one month gave no relief. The blood chemistry revealed a uric acid of 5.1 mg. (3 mg. is the upper limit of normal) and a nonprotein nitrogen of 33 mg. per 100 cc. The patient improved immediately on a low purine diet (Table 1).

How essential it is to be thorough! I had not suspected this to be on a gouty basis on the first examination. The case presented the tenderness on the sides of the os calcis so characteristic of toxic and metabolic painful heels. This case also brings home the point that the patient cannot be too young to have gout.

### BACKACHE

In an orthopedist's practice, the pain that is most difficult to relieve is backache. Some backaches are never amenable to relief, standing next in line to causalgia; in fact, some of them are causalgia.

Pain in the back may arise from the following:

1. Intervertebral disks:
 

Inflammation	}	Resulting in the so-called "intractable" backache.
Degeneration		
Protrusion		
2. Articular facets.
3. Bodies and their arches.
4. Ligaments:
 

Ligamenta flava.
The numerous ligaments that pass from ilium to sacrum, ilium to transverse processes, intertransverse processes, etc.
5. Muscles:
 

Fibrositis.
Myositis.
6. Extravertebral sources:
 

Visceral, genito-urinary, retroperitoneal lesions; sympathetic lesions, etc.
--
7. Prodromal to some acute infection:
 

Exanthemata.
Infectious diseases, influenza, infantile paralysis.

### PROTRUDED INTERVERTEBRAL DISK

*Case VI.*—A woman forty-two years of age was seen in April, 1939, because of pain in the small of the back of two months' duration and gradual in onset. She felt better in the morning. She had difficulty in straightening up after stooping, and complained of some pain down the outer surface of the right thigh. She had had lumbago in November, 1937. This condition had followed her lifting something at the office.

Examination disclosed no particular area of tenderness. Straight leg raising was suggestive. Her posture was poor. She was advised to wear a

reinforced corset, to take some short-wave diathermy and massage, and also to exercise to improve her muscle tone and posture. She was seen two months later and, at this time, it was noted that her posture was improving. She had been free from backache except for one acute attack which followed a lot of stooping. The pain lasted two weeks. She stood an automobile trip to the west coast very well. In April, 1940, she entered the hospital because of an acute attack which was going into its fourth week.

On examination at this time she seemed in acute pain, apparently had not slept much, and was unable to be quiet in bed. She was tender over the spinous processes of the fourth and fifth lumbar vertebrae. Straight leg raising (Goldthwaite) and Laségue tests were both quite positive (the sciatic nerve was tender wherever it could be palpated). Knee and ankle reflexes were present on both sides. Sensation was good, although she thought pin prick could be felt more acutely over the lateral side of the right thigh. Traction and opiates did not relieve her. An air cushion to relieve the fourth and fifth spinous processes from being touched relieved the pain most, but not enough so that she could sleep.

This is the type of pain that one associates with a root pain, the so-called *intractable* backache. The history of increasing severity in spite of treatment, localized tenderness to two spinous processes together with the referred pain down one leg are suggestive of a protrusion<sup>5</sup> of the intervertebral disk from between the fourth and fifth lumbar into the spinal canal. Five cubic centimeters of lipiodol were injected intradurally at the third lumbar interspace to visualize the canal. This showed a right-sided protrusion extending across center into the canal at the fourth and fifth lumbar interspace. In this connection it is interesting to note that in the last two days the patient had also been having pain down the left leg. Spinal fluid chemistry and cell content were within normal limits.

An exploratory operation was performed and the disk between the fourth and fifth vertebral bodies was found torn. The ends bulged into the canal and there was a free piece the size of the end of the little finger under the posterior longitudinal ligament. This was the cause of the patient's most acute attack, in which she rolled and tossed, and probably caused the free piece to shift to the left, causing the symptoms to cross to the left also.

The relief from pain after removal of a protruded disk is miraculous. Whether relief will be permanent in the above case I am unable to say. There were many frayed pieces and it was difficult if not impossible to get them all. One would suspect that the frayed ends would proliferate and at some future date cause a recurrence of the syndrome. The Mayo Clinic reports having reoperated in five such cases; there are no other reports of end results.

#### INFLAMMATION IN THE ARTICULAR FACETS

Inflammation in the articular facets<sup>6</sup> gives a picture similar to the above. The sciatica is not as intractable, nor is the course so long drawn out. The pain and stiffness in the back is quite like that of an arthritis in a major joint and the referred pain is due to the pressure of the joint edema on the



roots as they leave the foramina. Correctly taken x-rays will reveal the changes in the joint incident to the arthritis.

The majority of these patients respond to *physiotherapy* and *immobilization* and any measures that are found helpful



Fig. 3.—A, Start the tape as illustrated. Hold the body with the left hand and draw the tape quite tightly with the right hand. Three such tapes are applied, covering the area from the level of the trochanters to a plane 1 inch or more above the crests of the ilia (as in C and D). Tape is most easily handled in the form of a 10-yard roll 3 inches wide. Hold the end as in B and the wrinkling will be minimal.



Fig. 4.—Before the circumference is finished anteriorly (E) the pubic hair should be covered with some material as sheet wadding (Fig. 3, D). If a second circle of tape is covered over the first, the tendency to wrinkling and rolling is diminished. This is sufficient tape for a sacro-iliac sprain. If there is pain at the sacrolumbar, iliolumbar (or higher) in the spine, a pair of suspenders (E and F) should be applied before the second layer of tape is put on. G shows the limitation of motion in the spine acquired with such a taping. All the forward bending is rotation of the pelvis in the hip joint.

in arthritis. Occasionally the arthritis may be so refractory to treatment that a fusion is indicated and the root pain so severe that the joint in question should be resected. Steindler states that 90 per cent of the low back pains fall into the ligamentous and muscular pathologic group.

Case VII.—A young woman aged twenty-eight complained of pain in the back of one year's duration. She felt best in the morning; as the day wore on her back began to ache, more particularly in the small of the back. She was an office worker. Examination revealed a well built woman with fair posture. No tender areas were elicited. Motions of the spine were good and foot posture was good.

This pain comes on later in the day when the muscles tire and let up a little. Then all the stress and strain falls upon the next supporting structures, which are the ligaments.

This type of pain can be relieved by *improving the muscle tone*. The exercises that are required in college physical training courses will do. The *Klapp scoliosis exercises* (Surgical Clinics of North America, February, 1939, page 137) were prescribed for the foregoing patient. Steindler's<sup>7</sup> text contains some illustrations of Lovett's exercises, and they are not unlike the Klapp exercises.

This patient's symptoms subsided in a short time. In the so-called asthenic type of individual it may be necessary to have the patient wear a reinforced *corset* (cf. Steindler). For low back strain, the corset should come to the lower limits of the scapula. In more generalized cases the corset should come to the spine of the scapula. Both corsets should have shoulder straps. The staves should be extra strong bone or steel. It is sometimes helpful to tape the back (Figs. 3 and 4) as a test. If a patient gets no relief from the tape, she is not likely to find any in the corset.

If a patient states that a few days ago he fell down a few steps and the back has been hurting since, the chances are that it is a sprain and the treatment should begin with heat, massage and immobilization in the form of a back strapping or a corset.

#### LIGAMENTAL PAIN

The function of ligaments is to limit the range of motion of a joint. If they are called upon frequently to do so, they are subject to strain. If the force exceeds the physical strength of the ligament, there are minute tears and it is called a *sprain*. If the force continues, it becomes a *tear*. In more superficial joints one can detect sprains by localizing the tender area, by increasing the pain if tension is increased and decreasing the pain by relaxing the ligament. Sprains of the back can be diagnosed in the same way, although the ligaments are more deeply placed and hence cannot be accurately felt, but they should respond to relaxation and immobilization.

A tender area that has existed for a long time at the origin

or insertion of a ligament or fascial band or musculotendinous or tendo-osseous junction is called by some a chronic strain, by others a *fascitis*, and by still others a *myofascitis*. It is maintained by some that there is no such term as "myositis" in the sense that it applies to backaches or aches in any muscle. The pathologic feature is a proliferation of the interstitial tissue or fibrous tissue among the muscle cells. There is the myositis that turns into bone; that is a different problem. The etiology of fascitis is considered to be toxic. Albee maintains that these cases have a stasis of the gastro-intestinal tract which results in change of flora and the formation and absorption of products to which fascia is sensitive.

*Case VIII.*—A middle-aged man presented himself because of more or less continuous backache. It is made worse by working and he felt stiff in the morning. Examination revealed tenderness at the right posterior superior spine. Range of motion of the spine was good. Two injections of novocain and saline relieved him of his pain, and he remained free of pain in this area for four years. On two other occasions he has presented himself because of pain; once at the origin of muscles at the right twelfth rib and again at the insertion of muscles into the rib cage anteriorly. One injection into each has relieved him.

Other practitioners use only novocain. I felt that there was a local tissue reaction and that the novocain-saline solution created a hyperemia which helped heal the local disturbance. In fact, the early cases were treated with saline alone and the novocain was added to alleviate the burning sensation. The saline must be *hypertonic*. Three per cent saline and 2 per cent novocain are mixed. The amount injected is immaterial, 5 to 10 cc. usually sufficing. Exercises are of no material aid in this group of cases. General arthritic care is more helpful.

There is a group of patients, most often with pain in the back muscles, who, following exposure to draft, complain of pain in a localized area. On carefully palpating the area one can feel a knot, so to speak, as if a group of muscle fibers were in spasm. One deep heat treatment followed by a massage sends this type of a patient away "feeling like a new person." It is this and the following group that the irregular practitioners are most successful with.

A middle-aged man comes in, walking rather stiffly, who says that on the previous day, while playing golf, he was seized with a "catch" in his back and he points to the sacroiliac region. Motions in the spine are guarded. Straight leg raising is positive. There is tenderness at the posterior superior spine.

A good *baking* and *massage*, followed by the *manipulations* which Jostes<sup>s</sup> has so well illustrated, make this patient leave the office much more comfortable. The back should also be *taped*. After he is well over the attack, one may minimize the likelihood of a recurrence by teaching him to do his exercises regularly. It is in this type of case one hears so much discussion as to whether or not the sacro-iliac joint can slip serrations. The patient is usually an office worker and gets very little regular exercise. Whether or not the joint has slipped, the ligaments are below par in tone.

Certain of this group will complain of pain *referred down one or both legs*, more often in the course of the sciatic nerve. Steindler puts this figure at 30 per cent; he also has demonstrated that injecting the area of most severe or localized pain with novocain relieves and often cures the back pain.

#### FUSION

You ask "Which of these cases are you going to fuse?" None of them until all *conservative* methods have been exhausted. There is the bone defect group, like *spondylolisthesis*, which may be fused without trying conservative treatment. Most men feel that this is the group where fusion is certainly indicated. Yet one writer states that the unfused cases in his series have done better than the fused ones. Someone else has remarked that 70 per cent of the fusions, facetectomies, etc., have failed to relieve the symptoms. Nevertheless, we all have patients who received their only relief from surgical measures. The back is made up of many parts. The symptoms of each ailment have so much in common that it is difficult to diagnose which structure is at fault.

*Case IX.*—A young fireman presented himself because of pain about his knee joint. He had been struck on the lateral surface of the knee by a falling ladder. His surgeon had removed the external semilunar cartilage through a lateral incision. Examination revealed nothing abnormal: no tenderness, no limitation of motion of the knee, and the muscles supplied by the peroneal nerve functioned. The posterior limb of the incision lay over the course of the external popliteal nerve. During the period of observation the pain extended down to the foot. Could the nerve have been cut? Exploratory operation showed a normal appearing nerve. The insurance company denied any liability and discontinued disability payments. The man was a malingerer. Soon he developed foot drop. Some time later, without associated pain, atrophy began in the other leg. The diagnosis now was clear.

#### COMMENT AND SUMMARY

There are pains that we can find the cause for and can cure. There are other pains which we do not understand,

but suppression with novocain for a period at intervals seems to relieve them, sometimes permanently, sometimes temporarily.

Leriche attributes them to vasoconstriction by irritated sympathetic nerve fibers. In cases with spreading pain he has found edema of the nerve roots that supply the irritated zone. Does the lesion pass up the nerve and become a lesion of the brain and mind?

I believe that there is a basis for every patient's complaint. It is up to the physician to find the cause; it may be physical, it may be mental. There is no doubt in my mind but that the patient suffers real discomfort.

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## CLINIC OF DR. G. K. FENN

### ST. LUKE'S HOSPITAL

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#### PAIN ARISING IN THE CIRCULATORY SYSTEM: DIFFERENTIAL DIAGNOSIS AND TREATMENT

WHEN one prepares to hold a clinic on pain arising in the circulatory system one is at once appalled by the breadth of the subject. The circulatory system penetrates the entire body and, while some of the structures it serves are insensible to pain, most of them protest when they are deprived of their blood supply. This protest usually takes the form of pain. On the other hand, a too great blood supply may cause pain. So, wherever and whenever pain occurs in the body we must at least consider the *possibility* of circulatory causes. Often one can immediately eliminate the circulatory system as a primary factor, but we should at least *think* of the circulatory system in this connection.

Let us consider first the so-called *functional* disturbances of the circulation that are associated with pain. These may be divided roughly into two groups, the *vasoconstrictor* disturbances and the *vasodilator* disturbances. The most common of the vasoconstrictor disturbances is Raynaud's disease.

#### RAYNAUD'S DISEASE

Maurice Raynaud described in 1862 the striking local asphyxia and symmetrical gangrene that has since been known as "Raynaud's disease." Every practitioner of medicine is familiar with it and little will be learned about it that is not contained in Raynaud's original article. In recent years, studies have tended to show that there may be several etiologic factors that result in appearance of symptoms of Raynaud's disease. Dr. Johnson of our own Department of Medicine has collected and will shortly publish the account of a study of several cases. Johnson has apparently "cured" some of his patients but this cure was effected by vigorously treating a hitherto undiscovered syphilis or a severe secondary anemia.

These studies, and similar ones, would arouse the suspicion that Raynaud's disease is a symptom, just as angina pectoris is a symptom. It seems entirely possible that time may reveal the various underlying causes and bring about additional cures.

*Treatment* of Raynaud's disease today is not very satisfactory. Protective measures are employed in the milder cases. For the severe cases, sympathectomy seems to be the best available treatment.

The one thought I would leave with you about Raynaud's disease is this: Examine your patients thoroughly. Do not be satisfied to stop when you discover local areas of asphyxia that are symmetrically distributed. Correct any associated pathology that you may find in a careful examination. Remember the experience of others who have caused the Raynaud symptoms to disappear by correcting associated pathology.

#### ENCEPHALOMELALGIA

I can see that I am consuming too much time with a discussion of subjects of relative infrequent occurrence, but I must discuss one phase of the occurrence of pain when the blood supply is too great. You are all familiar with the burning and pain of erythromelalgia. At the recent meeting of the American Medical Association in New York, Dr. Horton of the Mayo Clinic described a unique headache that he called, I believe, "encephalomalalgia." Dr. Rowntree, half facetiously and at the same time altogether seriously, suggested that this condition be known as "Horton's headache." Dr. Horton separated these patients from the large group that had been labeled "migraine." He noted that the headache in these people occurred rather frequently, was very severe, was unilateral, and was accompanied by flushing of the skin and sweating. Through a brilliant bit of reasoning, it occurred to him that this phenomenon might be the reaction to an excess of *histamine*. His subsequent observations proved the correctness of this hypothesis. Since I returned from the New York meeting I have been on the alert for such a case, and I have one to show you this morning. This is the only one that I have been able to find so far and the patient has been good enough to return for exhibition.

*Case 1.*—The patient, Mrs. E. S., is thirty-nine years old. She came to the hospital about a month ago, with the complaint of headache associated with nausea and visual disturbance. There were a number of other general complaints which at first aroused a suspicion that there might be a neurogenic basis

for all of them. She was very insistent, however, about the disabling features of the headache, but seemed quite resigned to them. She had been told that she had migraine and the usual remedies had been tried. None of them were effective and she had been told that nothing further could be done.

The patient stated that the headaches occurred at least three times a week and sometimes they occurred daily. They were always unilateral, situated in the right temporal region. She stated that her right eyelid swelled during the attacks so that she could not see with the right eye, and that the whole face and neck were flushed during the headaches. Sometimes she perspired only over the affected side.

These symptoms seemed to fulfill all the requirements of "Horton's headache" save one. The symptoms must follow the subcutaneous injection of histamine. That is to say, this type of headache must be unilateral, must be of frequent occurrence, must be associated with flushing of the skin. All of these, however, may be associated with other types of headache. The one absolute prerequisite to diagnosis consists of the reproduction of the headache by the injection of histamine. Accordingly, this patient was given 0.5 mg. of histamine as a diagnostic test. In Dr. Webb's technic for this test, after injecting the histamine he would try to distract the mind of the patient by conversation about the war or the latest fashion, and hitherto all that had resulted was a lot of conversation that Dr. Webb did not particularly enjoy. On this occasion, however, in about fifteen minutes the patient no longer had any interest in the conversation. She had a headache. It was unilateral. There was flushing of the skin and the right eyelid actually was swollen. The patient stated that it was an absolute reproduction of the spontaneous headache.

There is only one reason for devoting this amount of time to a single type of headache but that reason is very important to the patient. These patients can be *cured* by correcting the histamine sensitization. Mrs. S. has controlled her headaches by the use of histaminase in the form of torantil. We propose now to desensitize her with histamine injections in exactly the same fashion that pollen antigen is used to desensitize hay fever patients.

So much then for pain of a functional nature due to circulatory disturbances. The field is a large one and has yielded meager results in cultivation. I believe the two instances discussed represent the most recent practical advances in our knowledge in this field.

#### THROMBO-ANGIITIS OBLITERANS

One of the most distressing types of pain that has its origin in the circulatory system is that caused by thrombo-angiitis obliterans. Although this disease was probably first described by Friedländer in 1876, the brilliant work and careful studies reported by Leo Buerger in 1917 resulted in the attachment of his name to the disease. This disease is most commonly confused with Raynaud's disease or with extensive arterioscler-



osis, but careful observation will easily distinguish it from either.

This disease offers an excellent opportunity to observe almost all of the disturbances of the peripheral circulation in the same patient. There are *arteritis*, *phlebitis* and *thrombosis* of both artery and vein. The patient usually comes to the physician because of pain in the leg or legs on walking. He states, as a rule, that this pain comes on more easily in cold weather. Indeed, occasionally one gets a patient whose sole complaint is that he has difficulty in *keeping one of his feet warm* during the cold weather. It has always been rather surprising to me that this difference in temperature should impress itself upon the patient. Almost invariably when patients with Buerger's disease are questioned, we find that they suffered from cold feet before pain appeared; but when both feet were equally cold they paid little attention to it. When one foot became cold and the other remained reasonably warm, this fact sometimes sufficiently impressed the patients so that they consulted the doctor.

The patients are relatively young—between twenty-five and forty-five—and so do not fall into the arteriosclerotic age group. Their pain at first is conditioned wholly upon exercise and is almost invariably worse on one side. These facts should differentiate it from Raynaud's disease.

*Examination* will show a reduced or absent arterial pulse in the affected area. The extremity will feel cold to the examining hand. Elevation of the extremity produces *blanching*, and there is slow return of color when the arm or leg is allowed to hang down. This is later followed by a purplish cyanotic tint that is quite characteristic. *Superficial phlebitis* occurs in a fair number of cases and often becomes a great nuisance. The frequent occurrence of superficial phlebitis should make us seriously consider Buerger's disease whenever we find such a phlebitis. Of course, later we find *ulceration* about the nail bases, *gangrene* of the fingers or toes, and later, *gangrene* of the entire extremity. Buerger's disease is said to be progressive but the rate of progression varies a great deal, and it seems reasonably certain that some cases are arrested. I show you the next patient to demonstrate the apparent *arrest* of a case of Buerger's disease:

*Case II.*—This is Mr. M. S., aged fifty, an American of British extraction. I mention this to refute the former idea that this disease occurred only in Russian or Polish Jews. Ten years ago, at the age of forty, this gentleman first consulted the doctor because of pain and coldness of the feet while walk-

ing during the winter. He had noted this during the past two winters but had had no trouble during the summer. Upon close questioning it developed that he had coldness of the feet before the pain appeared. He had taken to wearing woolen hose, when he previously had worn light weight hose, for a couple of years before he noted pain. There was considerable pain in both feet but it came on earlier and was definitely worse in the left foot.

The findings on examination of the patient ten years ago were not essentially different from those of today. There is no dorsalis pedis or peroneal pulse in the left foot. The right dorsalis pedis artery cannot be felt, but there is a much reduced pulsation in the right peroneal artery. When we elevate the feet you will note how rapidly the color changes. The left foot looks almost as if the blood had been expressed with a Martin bandage. Now if we ask him to sit up and allow his legs to hang over the edge of the table you will see that the color slowly returns. Watch the left foot closely, please. Note the purplish color begin to appear. Now you may see the purple, cyanotic and mottled appearance that is characteristic of this condition.

This gentleman has adhered very closely to his treatment during all of these years. Whether that is responsible for his present relatively good condition, or whether his disease has automatically ceased to progress, I do not know. Because of the rather unusually good condition of this patient, we entertained doubts of the correctness of the diagnosis. Two years ago a bit of muscle was removed from the calf of the leg and the microscopic examination showed the diagnosis to be correct.

*Case III.*—I show you the next patient, A. P., who has not been so fortunate. He was a foundryman whose pain appeared in both legs about six years ago, at the age of thirty-eight. He paid no attention to it and did not seek help until two years ago when gangrenous areas began to appear in the fourth and fifth toes of the right foot. A few years ago the right foot was amputated well above the ankle and you will see that the stump is ulcerated and angry-looking. Three of the toes on the left foot are now affected, and the outlook is not good. This is an example of what may happen in a relatively short space of time.

It is always difficult to treat a disease of unknown etiology. The cause of Buerger's disease is still unknown. It has been credited to heredity, infection, tobacco and a number of other causes but none have been proven. In fact, tobacco has been fairly well ruled out as a causative factor and the use of tobacco is denied the patient with Buerger's disease for a different reason. It is known that the use of tobacco causes constriction of the peripheral vessels and thus lowers the skin temperature. In Buerger's disease, our every effort is directed toward dilating the peripheral vessels, therefore tobacco must not be used by the patient.

*Protection of the feet* is a most important item of treat-

*ment.* Dr. Joslin has said that if the diabetic kept his feet as clean as he keeps his face, diabetic gangrene would almost disappear. This necessity is doubly true in Buerger's disease.

The remainder of the treatment, apart from the management of the complications, such as ulceration and gangrene, consists in an effort to *increase the circulation*. These measures are many and all of them should be employed at some time.

The most available method is *local application of heat*. This may be accomplished by placing an electric light in a cradle. Care should be taken to prevent burns. The temperature should not be allowed to go much above 100° F. Immersion of the extremities in warm water, as warm as may be comfortably tolerated, is helpful. Contrast baths, warm water followed by cold, is believed to be effective. There are numerous mechanical devices designed to increase the circulation locally.

*Alternate pressure and partial vacuum* enjoyed considerable popularity for a while. This is carried out in a specially constructed chamber known as the pavaex boot. Some doubt has been thrown on its effectiveness but it is worth a trial. One note of warning should be sounded. Pressure may be dangerous when infected or gangrenous ulcerations are present. Intermittent venous obstruction may be of value.

The benefit derived from the various attempts to augment the circulation is greatly dependent on the number of blood vessels that remain capable of dilatation. The occluded and thrombosed vessels cannot be greatly affected by anything, but the remaining vessels can be made to dilate and carry in an extra amount of blood. To this end *artificial fever therapy* is sometimes used. The injection of typhoid vaccine is the favorite method of producing this pyrexia. Insulin free pancreatic tissue extract has been used to provoke vessel dilation, as has muscle adenosine phosphate.

Finally, in well selected cases, *sympathectomy* has appeared to produce favorable results. Certainly the problem of Buerger's disease is not solved. At the same time, definite progress has been made and the future is somewhat brighter for those unfortunate persons who are afflicted with it.

#### PULMONARY EMBOLISM

One of the most tragic of vascular accidents is the occurrence of an embolism in the pulmonary artery. This accident so often occurs at the height of postoperative convalescence

and too often fatally terminates what appears to be an uneventful recovery. Operation is not the only *cause* of pulmonary embolism. It may follow thrombophlebitis from any source—fractures, congestive heart failure or coronary occlusion. It may arise from the most unexpected sources, as I shall show presently. It is usually the thrombophlebitic or postoperative (which is the same thing) embolism that produces pain and causes difficulty in diagnosis. This subject has especially engaged my attention during the past two or three years, and I am in great danger of talking too much about it. I shall try to hold myself within bounds.

The typical picture of a pulmonary embolism is that of *sudden, severe pain in the chest* associated with circulatory collapse. Sometimes, but not always, there is spitting of blood. If the chest pain is left sided or general, the question of a *coronary occlusion* is immediately raised. There is nothing in the clinical picture to aid in a differential diagnosis at once. The patient has pain in the chest, the blood pressure has fallen, he is pale and appears to be in shock. The heart tones are rapid and the breathing is shallow. All of these signs might be interpreted as meaning either pulmonary embolism or coronary occlusion. Within twenty-four hours it is usually possible to arrive at a differential diagnosis. In pulmonary embolism, localizing signs will appear in the lung. There will often be a patch of moisture where the infarct lies, and sometimes consolidation will be evident to the percussing fingers or to the stethoscope. A pleural friction rub may appear and often the x-ray will localize the pulmonary infarct. It is not the twenty-four-hour period that concerns us here, however. We are concerned with the differential diagnosis and the treatment of the immediate emergency.

I do not believe it is always possible to make a correct differential diagnosis at once. I show you here the record of a patient who presented this problem:

*Case IV.*—C. M., a man of sixty-six, had been operated on six days prior to his attack. Dr. H. E. Jones had removed an acutely inflamed appendix and recovery was proceeding uneventfully. On the sixth day following operation he had an attack of pain in the left chest. The pain was severe and crushing and was associated with shock. The blood pressure dropped from 152 systolic to 104 systolic. There was no cough or spitting of blood. An electrocardiogram was made on the day of the attack and a noncommittal tracing was recorded. It was advised that serial tracings be made to substantiate the diagnosis of a possible coronary occlusion. The patient had a similar attack on the following day and died. The autopsy showed no sign of coronary occlusion but there were multiple pulmonary emboli.

During the past two or three years I have cooperated with Dr. de Takats and his co-workers at the University of Illinois in an investigation of this problem of pulmonary embolism. The result of a portion of this investigation has been published, and I shall not describe the work here. I shall only say that this investigation has convinced us that death from pulmonary embolism is largely a reflex phenomenon. In only a few cases is it mechanical. We believe the reflex is carried by the vagus and affects both the lung and the coronary circulation.

We believe that the *treatment* of the immediate emergency is the use of *atropine* to block the vagal reflex and of *papaverine* to relax the reflex spasm of bronchioles and blood vessels and for its sedative effect.

*Oxygen* is used to overcome the asphyxia. *Aminophylline* intramuscularly or intravenously also acts as a dilator of blood vessels and bronchioles.

I shall read from the record of a patient to illustrate this type of therapy:

*Case V.*—Mrs. E. T., a thirty-six-year-old woman, was ten days convalescent from a cholecystectomy when she had a sharp attack of chest pain. Together with the pain there was cough and blood spitting. The patient immediately became very ill. She was pale and with sighing respirations. The pulse was weak and thready and the blood pressure could not be obtained. Dr. John Lindquist chanced to be in the ward when the attack took place. Within ten minutes of the onset of the attack the patient had received intravenously  $\frac{1}{2}$  grain of papaverine and  $\frac{1}{3}$  grain of atropine. Later she was given oxygen inhalations. Dr. Lindquist described the dramatic improvement in the condition of the patient following the medication. It was subsequently shown by x-ray and by physical findings that a pulmonary embolism had occurred. The patient has now fully recovered.

This is standard practice now in the treatment of pulmonary embolism and we believe we shall soon be able to report a considerably improved mortality rate. Furthermore, we no longer need worry about an immediate differential diagnosis between pulmonary embolism and coronary occlusion because nothing in this plan of treatment would be detrimental to a patient with an acute coronary occlusion.

#### THROMBOPHLEBITIS

The last patient I wish to show represents a sort of pathologic museum of vascular disease:

*Case VI.*—Mr. E. C., aged forty-six, is the shop foreman of a manufacturing company. In June of last year on the day before his vacation he bumped

his shin on a steel pan while walking through the shop. The injury caused him no concern and on the following day he left for his holiday. Four days after his departure he noted a sore spot at the site of the injury and when he examined the leg he could see a red linear swelling which he thought was a swollen vein. He did no traveling for the next three days and on the eighth day following the injury his ankle began to swell. He states that the redness and pain in the leg had not increased but the swelling of the ankle frightened him so that he curtailed his vacation and returned home.

Now let us stop and reconstruct the picture to this point. The patient clearly had a thrombophlebitis as a result of his injury. Thrombophlebitis occurs as the result of *local injury* to a vein. This trauma may be mechanical, chemical or toxic. The other causes of thrombophlebitis, such as venous stasis with pressure or an individual tendency to clotting (thrombophilia) need not be considered here. This man had a local mechanical trauma which was followed by the usual symptoms of superficial thrombophlebitis. These *symptoms* are *local pain, redness and swelling* of the vein. The vein can usually be palpated and has the feeling of a solid cord. There is swelling about the affected vein but no distal edema, as a rule, and there is superficial phlebitis. When swelling of the ankle occurred it indicated that the inflammatory process was progressing into the deeper veins. A progressive thrombophlebitis is very annoying and eventually may cause serious trouble, as is well shown in this patient.

When this patient returned home he was hospitalized, kept in bed with his leg elevated, and moist heat was applied. At the end of eight days the soreness and redness had disappeared, but there was still some swelling when the leg was allowed to hang down. Up to this point it would seem that this was a clear case of traumatic thrombophlebitis that had responded well to the proper treatment.

Looking at the situation in retrospect, the rapid progress into the deep circulation may have been worthy of a little more consideration, but at the time it seemed that here was a patient who had recovered from a thrombophlebitis with some obstruction in the deep veins that might easily be compensated for if treated with proper support and exercise.

The patient was sent home from the hospital with an elastic bandage applied to the leg and was told to be up and about. The following week he went to the doctor's office for an examination and things seemed to be in a satisfactory state. About two hours after his return from the doctor's office he had a sudden severe pain in the chest, spat up a little blood and collapsed. His next conscious recollection came about four days later when he found himself in an oxygen tent in the hospital. He had sustained a fairly massive pulmonary infarct and it was now obvious that the thrombophlebitic process had

not entirely subsided. He was in the hospital for seven weeks. He remained at home for an additional two months after his hospitalization. He then returned to work but his lot has not been a happy one.

Examination now shows swelling and induration in both legs. You may see varicose veins in both legs. The left leg, the one that sustained the injury, appears worse than the other, but the right leg has not escaped. Note the varicosities on the thighs and even on the abdominal wall. Note the two ulcers on the left leg above the ankle and the similar ulcer on the right leg. These ulcers have necrotic bases and extend down to the fascia.

With the whole picture before us now, it seems clear that the phlebitic process in this patient progressed to an unusual degree.

Following his pulmonary embolism, or perhaps even before the embolism occurred, the inflammatory process had progressed up the femoral vein, through the iliac and into the vena cava itself. I can see no other explanation of the bilateral involvement and of the varicosities in the abdominal wall. Whether this might have been avoided by more vigorous treatment in the beginning, no one can say. Fortunately, such extensive thrombophlebitis is rare.

It is very difficult to say when such a process has been *arrested*. I would say that patients with thrombophlebitis should be kept under appropriate treatment until all local signs of active inflammation have subsided and until the leukocyte count and the sedimentation rate returns to normal. I might add that I do not always meet these requirements in my own practice but I insist that they should constitute the criteria of arrest.

The *prognosis* in this case is not very bright. The treatment now is largely surgical. A long period of bed rest will be required to heal the ulcers following surgical treatment, and it is quite likely that the circulation is so impaired that the prevention of new ulcers will be difficult.

CLINIC OF DRS. ROBERT S. BERGHOFF, ANGELO S.  
GERACI AND DONALD A. HIRSCH

FROM THE HEART STATION, MERCY HOSPITAL-LOYOLA  
UNIVERSITY CLINICS

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THE RELIEF OF CARDIAC PAIN

WE have selected for our clinic this morning four patients, each with a distinctly different type of heart disease and therefore with a different type of pain. Since the subject of cardiac pain is of itself a broad and comprehensive one, we shall devote only a minimal amount of time and attention to the pathology, symptomatology, physical signs, diagnosis and prognosis. Dr. Geraci will begin by demonstrating the first case, stressing particularly the measures to be employed in combating or relieving pain in this patient's type of heart disease.

Before considering these four patients and their individual heart problems, however, I shall distribute among you these reprints of a clinic given in this amphitheater nine years ago by myself and published in the *MEDICAL CLINICS OF NORTH AMERICA*. You will note that our subject at that time was "Epochal Heart Disease." We pointed out in that clinic that if we divide human life into *three epochs* of twenty-five years each, the first epoch to run from birth to twenty-five years and take in childhood and youth, the second epoch to run from twenty-five to fifty years and include an individual's prime, and the third epoch to run from fifty to seventy-five years and include an individual's senescence, the study of heart disease lends itself nicely to such a division. Each epoch has its own distinctive and almost pathognomonic type of heart disease. Thus the first epoch has its rheumatic endocarditis; the second, syphilitic heart disease; and the third, coronary artery and heart muscle disease.

For our records and for the literature, we naturally follow the classification of the American Heart Association. For teaching purposes, however, and for a hurried kaleidoscopic



review of the four major and so-called "primary" or "basic" types of heart disease we still like to present heart disease in an "epochal" fashion.

Dr. Geraci will present as our first patient this young man. He will hold the protocol, physical signs and diagnosis to the most essential points and stress the matter of pain and its relief. I am calling your attention to the fact that this patient fits squarely into his age classification or epoch. Dr. Geraci will now demonstrate our first case:

#### FIRST EPOCH: RHEUMATIC HEART DISEASE

DR. GERACI: Our patient for this first clinical demonstration is a boy of thirteen who gives a history of having felt perfectly well up to two months ago, when the following symptoms appeared: pyrexia ( $102^{\circ}$  F.), asymmetrical joint pain with localized swelling, redness and tenderness—all preceded by a tonsillitis with all of the attendant local signs. The hospital record, in addition, reveals heart consciousness, tachycardia, a smoldering fever and distress over the entire precordium, which is stationary and not referred.

Before discussing this pain, its mechanism and the measures employed for relief, I wish to stress the pertinent objective findings which are requisite to a *diagnosis* of rheumatic heart disease. In addition to the history, physical signs and symptoms previously mentioned, this patient reveals a mitral systolic murmur, heard best at the apex, with an increased right ventricular measurement of 4.5 cm. as against a normal of 3.25 cm. and normal findings of the left ventricle (8 cm.) and aortic width (4.5 cm.). These percussion measurements were verified by teleoroentgenography.

At this point I should like to digress for a moment and impress upon you the diagnostic importance of the *configuration* of the heart in rheumatic heart disease. Whereas the textbooks leave the general impression that the time of a murmur plus its maximum intensity and its general qualities are self sufficient to assure a correct differential diagnosis (for example, in mitral insufficiency a systolic apical murmur, in stenosis a presystolic apical murmur, in aortic insufficiency a diastolic basal murmur, and in stenosis a systolic basal murmur) this does not work out practically. The timing of a murmur in actual practice is not so simple. In fact, in some instances it may be complex and confusing. Each type of endocardial lesion, however, is associated with a very definite alteration of the contour of the heart. Thus, for example, the

diagnosis of mitral stenosis is made relatively simple and accurate by eliciting the characteristic contour; to wit, an increase in the cross diameter of the heart with the right ventricle supplying the major portion of the hypertrophy. In addition, the left auriculoventricular concavity is transformed into a convexity. In contradistinction to this mitral configuration, we have one for aortic disease which is just as characteristic and diagnostic and consists essentially of a left ventricular hypertrophy, being much more pronounced when associated with an aortic insufficiency than with an aortic stenosis.

To come back to our patient, his pulse rate is 100 and is regular. Even though only two months have elapsed and this appears to have been his first attack, the left auriculoventricular concavity shows a tendency to a straightening at this time.

In the first twenty-five years of life rheumatic heart disease comprises 90 per cent of all organic heart disease, the remainder being congenital and the conduction disturbances. Etiologically, acute rheumatic fever is responsible for over 50 per cent of the cases; the remainder are due to chorea, possibly scarlet fever, and atypical rheumatism. At any rate, acute valvular heart disease seems to be of streptococcal origin.

To *recapitulate*, we have in this instance a young boy, aged thirteen—a typical case of acute rheumatic endocarditis due to acute rheumatic fever. The patient's acute rheumatic fever is typical in every respect: with few if any prodromal symptoms he suddenly presents the following clinical picture: sore throat, pyrexia, general body sweating, involvement of the larger joints asymmetrically and asynchronously, a leukocytosis, increased sedimentation rate and heart symptoms. His heart symptoms are as follows: heart consciousness in the guise of a tachycardia and a forceful heart, dyspnea, approaching orthopnea and pain.

It is not my purpose this morning to discuss with you acute rheumatic fever, nor acute rheumatic endocarditis, nor even this boy's problem in its entirety, but rather I should like to discuss with you the subject of *cardiac pain in general*, particularly its mechanism and methods of relief. We might begin by asking the following questions: Is cardiac pain a frequent symptom in acute rheumatic fever? What is its mechanism and what measures are employed for its relief? Clinically, according to Black<sup>1</sup> cardiac pain is seldom seen except as an angina and as an associated pericarditis. In

about 50 per cent of the cases of acute rheumatic fever fibrinous pericarditis clinically diagnosed exists, which probably produces the cardiac pain due to involvement of the sensory nerve terminals in the epi- and endocardium. Tissue examinations have shown as many as 300 of these sensitive nerve terminals to the square centimeter. Postmortem, however, fibrinous pericarditis is quite common. This might mean that pericarditis exists in a large percentage, subclinically; hence there is little or no pain. Cardiac pain due to mediastinal lymphadenitis is rarely seen.

In about 40 per cent of cases the *abdominal syndrome* is observed, and its mechanism has not been definitely established although there are adherents to the theory that the vascular bed of the gastro-intestinal tract becomes the reservoir when the heart begins to show signs of failure, with the liver especially becoming noticeably enlarged from back pressure. Others believe that systemic inflammation spreading by way of the blood stream to the gastro-intestinal tract by selective affinity or specific toxic action is the cause of the pain, possibly due to involvement of the sensory nerve terminals. Cardiac pain can be evoked in any region supplied by sensory terminals through application of adequate mechanical and chemical stimuli. *Mechanical* stimulation of the endings in the myocardium or vascular sheaths could conceivably arise through extreme expansion of the vessels by high internal pressure, or contraction of the vessels by chemical or nervous means or by periodic dilatation of an ischemic area or finally by compression of scar tissue. *Chemically*, it would appear that the stimulus for pain is a metabolic product which can readily diffuse into the blood stream and, on reaching a certain concentration, results in pain.

For the *control of pain*, aspirin and its salicylates seem to be the most effective agents, with codeine and paregoric as of second choices. Aspirin, in oral doses of 60 to 90 grains daily according to the age of the patient, seems to be the most effective medication and should be combined with sodium bicarbonate to lessen gastric irritation. Its exact method of action is not thoroughly understood, but its analgesic effect and the effect on the pyrexia is very gratifying. When nausea and emesis exist, the medication is administered in double doses in a thin starch retention enema for a few days until these distressing symptoms subside. Salicylates have been used, but with less effect.

Codeine, in doses appropriate for the age of the child, is

used orally and less often hypodermically. This is preferred to morphine because it is not habit forming and also because of the undesirable effects of morphine on the bowel. Purgative is the least desired of the agenda discussed.

DR. BERGHOFF: I believe Dr. Geraci has considered the subject of cardiac pain, as encountered in rheumatic endocarditis, about as thoroughly as the brief space allotted him will allow, and in summary it might be well to emphasize the following points:

1. The differential diagnosis between mitral stenosis and mitral insufficiency, and between aortic stenosis and aortic insufficiency, is greatly simplified by a comparative consideration of the configuration of the heart and the type of hypertrophy.

2. Cardiac pain in acute rheumatic fever is usually due to an associated fibrinous pericarditis.

3. The simple remedies for the relief of cardiac pain are usually effective and self sufficient.

Dr. Hirsch will present the next case and take up with you the symptom of pain as encountered in this type of heart disease:

#### SECOND EPOCH: SYPHILITIC HEART DISEASE

DR. HIRSCH: We now come to that period of an individual's life in which he is the most productive, and in which there should be no major or primary form of organic heart disease. This of course assumes that the person was given a perfectly normal heart at birth and that he was spared the tragic cardiac sequelae of rheumatism or its type of infection. None of us can stay the process of growing old; but, properly educated, all of us can avoid contracting syphilis, and once syphilis has been wiped out there will be no need for a discourse on the cardiac complications of the chancre. It is true that, today, our records are proving that adequately treated cases of syphilis are showing an appreciable reduction in the incidence of cardiovascular manifestations. Perhaps it is too much to expect that cardiac syphilis will some day become such a rarity that it will be a medical museum collector's subject.

We are fortunate in being able to present a very typical case of cardiovascular syphilis. This patient, a forty-eight-year-old salesman, was first sent to our Heart Station three and a half years ago. His story at that time was as follows:

For the previous six to ten months the patient had noticed substernal discomfort on inconsequential effort; this discomfort was fleeting and was limited to the submanubrial borders. It then became slowly but progressively

more intense and more frequent and occasionally would awaken him at night. Close questioning did not reveal any radiation to the jaws, neck, or along the course of the left brachial plexus. The patient then began to notice nocturnal palpitation which at times would accompany these attacks of substernal pain. The pain and palpitation were dismissed by him, but when they became quite severe and he began to experience dyspnea as another symptom, he decided to seek medical aid.

The pertinent features of the case at this time were a free admission of gonorrhea when the patient was about nineteen years of age and a penile chancre at about twenty-three years of age. This sore had been accurately diagnosed but insufficiently treated. He had had what he described as a few "shots" in the arm and a few mercury unctions, and because the sore disappeared he had felt that there was no further need for treatment. Then, about twenty-five years later, in what we call his second epoch of life, he was examined and these were the pertinent features:

1. A positive blood Wassermann and Kahn.
2. An increased retromanubrial dullness over the area of the aorta upon percussion, and a left ventricle within normal limits.
3. A teleroentgenographic confirmation of an aorta which had enlarged to 6.5 cm. across the ascending portion, and a left ventricle which was proved to be within normal limits.
4. A soft systolic murmur over the base of the precordial area.
5. A suggestion of the typical bell-like accentuation of the second aortic sound.

The *diagnosis* was an early syphilitic aortitis.

This patient had therefore been very lax in his treatment and now we find a progression and extension from the initial cardiovascular lesion of simple aortitis to an aneurysm of the ascending portion of the aorta. The *objective examination* now shows:

1. Again, a positive serology.
2. An aorta which is now 8.5 cm. across the ascending portion when examined teleroentgenographically. The left ventricle has remained within the normal borders.
3. The systolic murmur which is now much more pronounced.
4. A definite metallic accentuation of the aortic second sound.

*Subjectively*, there is severe, sharply localized, submanubrial pain which is exacerbated on even mild mental and physical excitation. The dyspnea, which only occasionally accompanied the pain in the early stages, is now a very constant feature. The above two symptoms have so disabled the patient as to limit his activity to a bare minimum.

If we remember the *basic pathology* of cardiovascular syphilis, we recall that it is a mes-aortitis of a chronic productive inflammatory nature. The intima shows many radiating retractions with thinning of the walls, leading gradually to a leather-like appearance of this coat. From the pathologic

features we take our cue to explain the progression from the early aortitis to the present aneurysm. The diseased aortic wall cannot withstand the constant force of the blood against it and it is forced to dilate. However, if a necrotic process permits the blood to be forced between the layers of the aorta, a sacculated aneurysm will be the result. If you noticed, in this case there was no appreciable increase in the size of the left ventricle. A competent set of aortic values and aortic ring have made an increased left ventricle unnecessary. However, when the aortic valve becomes incompetent, as clinically evidenced by the signs of an aortic regurgitation, then left ventricular hypertrophy ensues. An understanding of the pathology gives us a clear picture of the less frequent coronary ostia involvement, for in this instance the puckering of the lining of the aorta will occlude to various degrees the openings into the coronary arteries and give us the classical picture of coronary insufficiency.

To *sum up* briefly then, I have presented a case of early cardiac syphilis which has progressed from an aortitis to an aneurysm of the ascending portion of the aorta. The diagnosis is compatible with the early signs and symptoms of cardiovascular syphilis as described by one of us (R.S.B.<sup>2</sup>) and by the Co-Operative Clinic groups<sup>3</sup> and so ably presented by Stokes and Anderson in the July 1937 issue of this same publication. In brief they are:

1. Teleoroentgenographic and fluoroscopic evidence of aortic dilatation.
2. Tympanitic bell-like tambour accentuation of the aortic second sound.
3. History of circulatory embarrassment.
4. Increased retromanubrial dullness.
5. Progressive cardiac failure.
6. Substernal pain.
7. Paroxysmal dyspnea.

This case has given me the opportunity to present a sketchy resumé of cardiac syphilis in which the outstanding and earliest symptom has been pain. The discussion of that pain is my allocated task. The *mechanism* and *relief of that pain* are important considerations of clinical interest. First, we must, from the work in anatomy, seek the possibility of pain in the cardiac nerves. We know the vagus nerve is vital to the heart, but, too, we know that the vagus does not possess pain fibers. Therefore we can eliminate that nerve in the causation of cardiac pain. Inasmuch as the discussion of the mechanism of pain in cardiovascular syphilis has been rather meagre up to date and the exact mechanism has not been de-

terminated, we hope that a rational speculation at this point will lead to healthy stimulation of further work on the subject: We do know that pain from the heart passes over the cervical sympathetics with some fibers through the first to fourth thoracic dorsal sympathetics, for alcohol injections of the thoracic sympathetic ganglia will relieve this pain. It seems perfectly plausible to me that increased width of the aorta will cause pressure stimulation of these fibers which register in the pain center in the brain. However, in the upper portion of its course, the ascending aorta is overlapped by the anterior margin of the right lung and right pleural sac. A marked right-sided increase in the ascending arch may encroach upon these structures and give rise to symptoms which may direct one's attention entirely away from the heart. The right half of the deep cardiac plexus, which constitutes the right or anterior coronary plexus, reaches the heart alongside the ascending aorta and is distributed to the heart substance in the course of the right coronary artery. Sizable dilatation of the ascending aorta surely must lead to pressure stimulation of this plexus. Then, too, huge aneurysmal enlargements of the ascending aorta encroach upon adjacent structures in the superior mediastinum.

As the *relief of pain* anywhere in the body is of paramount importance to the patient, so it is here. I refer to the pain in cardiac syphilis *per se* and wish to leave the coronary portion of the story to be discussed by Dr. Berghoff. The outstanding feature, of course, in every discussion of syphilis or its complications is its *prevention*. If prevention has been neglected, early diagnosis and vigorous sufficient treatment are essential. It is true that many a man or woman may deny the existence of a chancre, and they may be perfectly honest in their story. But we must not forget that probably 25 per cent of all penile chancres are intra-urethral and many women may carry a chancre deep in the vagina without being aware of it. To overlook these possibilities may lead to tragic consequences later in the life of the patient. We are not in entire accord with those who feel that syphilitic aortitis cannot be diagnosed until the complication of an aortic regurgitation presents itself. We feel that with careful attention to details plus the use of all the diagnostic procedures at our command, we can ferret out many early cases of syphilitic aortitis which might be overlooked. If we can make the diagnosis at the point of simple aortitis, we feel that we can do much to delay at least the more severe complications.

The *drugs* of choice are the heavy metals and potassium iodide. Extreme caution must be observed with the use of the arsenicals, but we feel that very small doses of neo-arsphenamine in slowly graduated increases will be tolerated in these cases of early syphilitic aortitis. Potassium iodide in graduated doses up to the point of tolerance has proved to be of value. Bismuth in graduated doses can be given without the potentialities or the danger existent with the arsenicals. For the pain itself, we have started with the salicylates plus the barbiturates and progressed to codeine by mouth in sufficient strength as the case demands, and only with great restraint do we finally admit the patient to the opium group. We feel that his illness will be prolonged, and for that reason we withhold morphine as long as possible to give him the most relief possible, and we do not wish to reach his tolerance too soon.

DR. BERGHOFF: Before introducing and discussing with you the next two patients and their individual heart problems, let me summarize very briefly the points brought out by Dr. Hirsch:

1. The early diagnosis of cardiac syphilis, before the advent of aortic insufficiency, is feasible, practical and important.
2. The pain in uncomplicated syphilitic aortitis may be due to pressure on the cervical sympathetics.
3. For the relief of pain in cardiac syphilis, the iodides and bismuth salts are safe; mercury and the arsenicals should be used with caution.

### THIRD EPOCH: CORONARY ARTERY AND HEART MUSCLE DISEASE

My associates have up to this point demonstrated and discussed with you heart disease in youth (rheumatic endocarditis) and heart disease in middle life (syphilitic heart disease). This brings us up to the third epoch of life, *senescence*.

Using these next two patients and their distinctly different heart problems as *media*, let us consider coronary artery disease, and more particularly the symptom of pain as encountered in this type of heart disease.

#### CORONARY ARTERY DISEASE

Mr. A. C. B. is a white male, aged sixty-one, occupation clerical. He is married and has three children and one grandchild. His habits have been moderate and he denies having had venereal disease. He is mild mannered, of happy disposition, an extrovert, and distinctly not introspective or neurotic. He is very cooperative and gives in brief the following history:



His past, from a medical standpoint, is more than ordinarily negative and inconsequential. He has had since childhood no serious medical illnesses and no major surgery; in fact, he has not been confined to bed for a period of one week for thirty years.

His story about his ancestors, however, is rife with interest. Listen to this: His father was a lawyer and a successful one, and up to and including his fifty-seventh year, while not a robust individual, enjoyed excellent health. From then on, however, until his death at the age of fifty-nine he had periodic attacks of severe cardiac pain, which were relieved by rest and "a tablet under his tongue." He died, so our patient tells us, suddenly in a cardiac attack, presumably of coronary origin. This patient and his father were of similar stature and within 5 pounds of the same weight; both had blue eyes, fair skin and hair of the same color. Of even greater significance is the following statement: "Except for the difference in our ages, my father and I could have been twins. We thought alike on most subjects, we liked similar foods, places, people and things, and even the pitch of our voices was so similar that Mother had difficulty in differentiating them." But his family history is not yet complete. He says that his paternal grandfather, whom he remembers quite well, resembled his own father physically in most details and died at the age of sixty-two of heart disease preceded by several years of attacks of cardiac pain and asthma of brief duration, relieved by an inhalatory drug.

I give you gentlemen this powerful and significant family history a bit out of turn before reading from the protocol our patient's story of his own present complaints, which, as you may well anticipate, have to do with his coronary arteries, simply to stress a bit later the importance of *heredity*.

CHARACTER OF THE PAIN.—Our patient describes his present physical ailment as follows: Two years ago, at the age of sixty, he began to experience vague yet definite discomfort in his left chest. He hesitates to define this discomfort as pain, particularly when compared with the very definite and severe pains he has experienced later. He does say, rather significantly, about this early discomfort of two years ago, however, that it was brought on and aggravated by physical effort and mental excitation. It was brief in duration, disappeared quickly upon rest and quiet, and occurred at intervals of three to four months. Eight months ago (November 7, 1939), at the end of a rather trying day associated with numerous annoying details, and while running for a bus, he experienced his first real pain. This he describes as *excruciating* in intensity, *precordial* in location and referred into his jaws, *vise* or *cramplike* in character, disappearing after a few moments of rest and with no medication. He is positive of the following important details: (1) He did not break out into a sweat. (2) He was not conscious of his heart's rate or rhythm. (3) He had no gastric distress, such as belching or nausea. (4) On arriving home an hour later, he was no worse

for his experience, and after a hearty supper he went to bed and had his usual good night's rest and the next morning went back to work.

So far the story, with the diagnosis, is quite simple. This man unquestionably had a coronary episode, a rather typical attack of angina of effort, which relieved itself after a few moments of rest, without any direct medication. From here on, however, his story grows more interesting and a bit more complex and speculative. Since that attack on November 7 of last year, he has had progressively more frequently similar though milder attacks, so that, during the month of May, in spite of protecting himself as much as possible by slowing up physically and mentally, he cannot remember two consecutive painless days.

The pertinent question now arises, *Is this patient having daily attacks of angina of effort, and if so, what is to be done about it?* If, for example, instead of having repeated attacks of coronary spasm, he has suffered an occlusion of a minor branch of the left or right coronary artery, then our course of treatment is as simple as it is drastic. However, his story does not suggest a coronary occlusion.

Let us now review this patient's physical and laboratory findings for a moment. The former are essentially negative. His heart is normal in contour and size, his valves are clear, his rate varies from 70 lying to 76 sitting and 78 standing, and the rhythm is regular. The heart tones, too, are distinct and with a sound volume. His blood pressure on both arms is systolic 134 and diastolic 88. His heart dimensions are aorta, 4 cm.; right ventricle, 3.5 cm.; and the left ventricle, 8 cm. Accordingly, you will agree, from a physical standpoint his heart as an organ is normal. The electrocardiogram, while not normal, is not very helpful. It shows considerable QRS slurring, a high take off T in the second lead and left axis deviation but definitely no evidence of present or past infarction.

Now let us see where we stand at this point. We have an individual, aged sixty-one, who has inherited from his father and his father's father build, stature, coloring, idiosyncrasies, similar likes and dislikes, pitch of voice—and dare we not include coronary narrowing, since all three generations from the story had similar episodes and two of them apparently had coronary deaths?

**Treatment.**—We come now finally to the most important question—most important to our patient at any rate, How

shall he be treated, not only for the relief and avoidance of his pain, but to provide a decade or two decades of life to carry him on beyond his grandfather's sixty-two and his father's fifty-nine years?

We are not in this instance primarily interested in the relief of the paroxysms. As a matter of fact, he has learned that  $\frac{1}{100}$  grain of nitroglycerine under his tongue will bring him that relief quickly. Our problem, as before stated, is to *prevent* the occurrence of these attacks and beyond that, if possible, to increase his life expectancy. We are anxious to disprove the axiom which insists "No man can hope to live longer than the impetus of the germ-cell from which he sprang." Accordingly, with the prevention of these paroxysms as our first interest, we say to ourselves that this man with his story of daily attacks of cardiac pain of coronary origin must be treated as drastically as though he had suffered an acute occlusion of a coronary twig. We give him a thorough understanding of his situation and explain that his complete cooperation is essential, and then we institute a prolonged period of absolute bed rest. In his case, we kept him at bed rest for eight weeks and shaded that off with another four weeks of graded exercise before allowing him to return to his former habits and occupation. In addition to providing physical and mental rest and a moderation of his dietary and other habits, we gave him a daily capsule containing 3 grains of aminophylline and  $\frac{1}{2}$  grain of phenobarbital at bedtime without interruption.

He has just completed ten weeks back at his desk without a single recurrence of pain or any precordial distress. While he still remains an extrovert and in no sense has become introspective or melancholy, he has developed a calm, apathetic mental attitude toward inconsequential and trivial events which formerly upset him. We have insisted that he become more selfish, consider himself and his own comfort more, and be less intrigued with the concerns and misfortunes of a topsy-turvy world; and, gentlemen, he is plodding along to a longer, healthier and more tranquil life.

#### HEART MUSCLE DISEASE

I shall discuss with you now the fourth and last patient selected for our heart clinic this morning, Mr. G. H. K., a white male, aged seventy, who presents the following problem:

*Current History:* Eight months ago, while at work, and after a light but hurried lunch, he decided to spend a half hour in a moving picture theater be-

fore returning to his office. He felt as well as usual and was not unduly tired. Suddenly, while thoroughly relaxed and under no emotional strain, he experienced a severe substernal pain, "crunching in character," followed almost immediately by profuse sweating, heart consciousness and fear of impending dissolution. He was helped from the theater and taken to the hospital in an automobile. His pain increased in intensity and all of his symptoms became aggravated until the hospital Resident provided relief through hypodermic medication.

Now this man's story of his heart episode is so classical that it renders the diagnosis of acute coronary occlusion with myocardial infarction both simple and definite. The only atypical point in his story is his insistence that he never previously had experienced any precordial distress. We know that as a rule one or more anginal seizures precede an acute occlusion. His was an exception to prove the rule.

His past and personal history are irrelevant. His ancestral history, while not as positive as the previous patient's, reveals that his mother and one brother had repeated attacks of cardiac pain and died apparently coronary deaths.

**PHYSICAL FINDING.**—The physical findings, particularly cardiac, eight months ago at the time of the patient's attack, were significant, in contrast to the entire absence of abnormal heart signs in our previous case, and were as follows:

1. The most impressive cardiac abnormalities were the rate, rhythm and tonus. Before the institution of treatment his rate while lying in bed was 130 per minute, the rhythm an auricular fibrillation, and the heart tones so feeble as to be barely audible. There were soft systolic murmurs over both the base and apex of the heart. The blood pressure was systolic 108, diastolic 40.

2. The patient's general condition was unsatisfactory, his body was cold, clammy and wet, and he was plainly in shock. His outstanding and persistent symptom was a severe precordial pain, which now was also referred into his neck and left shoulder, and a gradually developing dyspnea.

**Treatment of Pain.**—Because pain was his predominant symptom, and because our clinic this morning is built around the subject of the relief of cardiac pain, I will confine my remarks from here on to that phase of his treatment.

He was placed at absolute bed rest and given opiates quickly and freely. His records show that morphine sulfate (grains  $\frac{1}{2}$  by hypodermic) was followed by  $\frac{1}{4}$  grain by hypodermic every four hours for sixteen hours. He was thus given  $1\frac{1}{2}$  grains in the first twenty hours following the occlusion. His second hospital day found him still suffering from a pain

not quite so intense but appreciable. Because his dyspnea had become a formidable and distressing symptom, he was placed in an oxygen tent, and morphine sulfate was continued at the rate of  $\frac{1}{4}$  grain every six hours, or a total of 1 full grain in the ensuing twenty-four hours. His third hospital day found his general condition somewhat improved. He had overcome his initial shock, his body was warm, his heart rate had slowed to a precordial count of 100; but his rhythm and tonus remained the same, his dyspnea was under control and he was resting satisfactorily. His pain, however, persisted. Accordingly his entire routine was maintained and he again received morphine sulfate, grains  $\frac{1}{4}$  by hypodermic every six hours, or 1 full grain in twenty-four hours.

He began his fourth hospital day satisfactorily, with his general condition improved, his heart tones more promising, his dyspnea controlled by oxygen and his pain distinctly diminished. At this point we made an important change in his management. We substituted *tincture of deodorized opium* for the morphine sulfate and gave the new drug freely. He received 10 minims every two hours for ten consecutive doses, or 100 minims in all. This substitution not only controlled his pain completely, but gradually ushered him out of his morphine "fog." In twenty-four hours the dose was decreased to 80 minims in twenty-four hours, then to 60 minims, and at the end of the first week to 40 minims. The dose of 40 minims was continued uninterruptedly for six weeks, not for the control of pain since that had ceased to be a problem at the end of the first week, but as a general sedative.

This patient made an uneventful and uncomplicated recovery and left the hospital at the end of ten weeks. However, two months later, or roughly eighteen weeks after his original occlusion, he returned with the following complaint: a severe constant aching in the left shoulder and upper arm with an occasional "tingling" in the fingers of the left hand. This aching or soreness, we were told, was present all day, both while he was at rest and while physically active, and even interfered with his sleeping. A cardiac survey at this time was entirely satisfactory, and the patient felt well in every other respect.

Acting on the assumption that his pain was of neuritic origin, diathermy and inductotherm treatments were prescribed. The results were only partially satisfactory. And, gentlemen, here comes an interesting observation: We instructed this man to take  $\frac{1}{100}$  grain of nitroglycerine sub-

lingually three times a day on the theory that since diathermy, heat and the inductotherm therapy had not proved effective, possibly his pain might be hooked up with his previous myocardial infarction, and he immediately experienced a marked relief! His left shoulder ceased aching—first for hours at a time, later for days, and finally the pain disappeared entirely. We have in our records seven similar instances of partial or complete relief of pain.

#### SUMMARY

In conclusion, I should like to summarize briefly as follows:

1. In acute angina pectoris with oft repeated attacks of coronary pain, even in the entire absence of evidence of occlusion of a coronary twig, treatment as radical and extensive as in acute coronary occlusion is both indicated and effective, as demonstrated in the first case I discussed with you this morning.

2. For the relief of severe and persistent coronary pain in acute coronary occlusion with associated myocardial infarction, morphine in large doses is the drug of choice.

3. After the pain in myocardial infarction has been partially controlled, tincture of deodorized opium is a valuable drug and can be used freely and over a protracted period of time.

4. In the so-called "post-occlusion neuritides," the coronary dilators, nitroglycerine and later aminophylline, have in our opinion theoretical value.

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## CLINIC OF DR. WALTER R. FISCHER

### ILLINOIS MASONIC HOSPITAL

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#### RELIEF OF PAINFUL FEET

SUCCESSFUL achievement in this field is directly dependent upon a knowledge of anatomy of the lower extremity, including a comprehensive idea of the normal variations in structure. Of equal importance is a knowledge of physiology, including the mechanical action of the locomotor system, and a knowledge of pathology covering the lesions of extrinsic as well as intrinsic origin that affect the foot. There is no short cut to this fund of knowledge that must be acquired by the physician who anticipates treating successfully the multitude of complicated conditions that present themselves in painful feet. This clinic is essentially a presentation of cases along with a discussion of treatment. Information concerning the anatomic, physiologic and pathologic factors not sufficiently explained must be gained from textbooks on the subject.

**PATHOGENESIS.**—The human foot is a burden-bearing structure and is actively used in locomotion. The effects of weight and strain have a profound influence on all pathologic conditions that arise. The effects of use or function may be the sole origin of foot disturbances or may be closely interwoven with the changes brought about through disease or injury. Cases of foot disturbance do not appear before the physician classified as to strains, deformities, vascular faults or skin lesions, but arrive in a helter-skelter fashion that in most instances taxes the diagnostic ability of the physician concerned. Therefore, one must have considerable preparation in the fundamentals concerning the human foot if he is to expect success for long in obtaining relief for patients with painful feet.

Tersely speaking, the troublesome foot can be explained by one or more of the following three factors: (1) variations in structure present at the time of birth that are not consistent with the severe usage to which the foot is subjected through-



out life; (2) the manner in which the foot is used including the influence of injury and disease; (3) the deleterious influence of wearing apparel.

The factor of *structural variation* must be given careful consideration in the analysis of every case. Some feet are much more suitable structurally for locomotion and weight-bearing than others. The foot with the less suitable structural arrangement is called upon for the same amount of work as that required of the more ideal type. Thus, trouble may arise purely as a result of the variation in structure, even though such variation is well within the realm of what is termed "normal." Obesity, excessive use and trauma are additional elements that may be combined with the variant structure and lead to the production of pain.

The *manner of using the foot* can be held accountable for the cause of foot disturbances when such use in standing or walking has been excessive. The rapid increase of weight that occurs in children during growth and in women during pregnancy, the toxic effect of certain systemic diseases on the muscles of the legs and the presence of peripheral vascular disease are examples of conditions that act alone or together with the use of the foot to produce the onset of changes that ultimately end in the production of the troublesome foot.

*Wearing apparel* (shoes and hose) becomes a sole or contributory factor to discomfort when it interferes with natural use by limiting the room for the foot, by interfering with stability and by altering the distribution of the weight.

#### FREIBERG'S DISEASE

*Case I.*—Dr. H. S., aged forty-three, a dentist, complained of pain and swelling in the region of the second metatarsophalangeal joint of the left foot. He gave a history of having hurt the second toe of his left foot at the age of fourteen when he kicked an object. He had been free from symptoms until this recent local pain and swelling appeared. Examination revealed swelling and tenderness about the second metatarsophalangeal joint. Upon palpation one could feel an enlarged, hard, irregular, mass at the distal portion of the second metatarsal bone. The roentgenogram (Fig. 5) revealed a distinct partial flattening and roughening of the dorsal aspect of the articular surface and head of the second metatarsal, with thickening of the shaft. In the anteroposterior view the distal end of the bone appeared slightly mushroomed, widened and irregular. The general health of the patient was good and there were no other joint symptoms.

This condition was described by Freiberg and since then has been commonly called "Freiberg's disease." It is supposed due to some form of trauma, or trauma associated

with a disturbance in circulation, with resulting aseptic necrosis during adolescence before the epiphysis has fused. Regardless of the etiology, the symptoms are unquestionably the result of use in the presence of a roughened joint surface, or to inflammatory changes following excessive strain on the joint. Thus the primary indication in treatment must be for rest of the affected part. This can best be accomplished by complete rest off the foot or by the application of a walking iron with a light cast to the leg and foot, so that the patient can be ambulatory. Even in cases treated in this manner the symptoms are prone to return as a result of the same irritation



Fig. 5 (Case I).—Roentgenogram of left foot showing changes in metatarsal II.

that produced them in the first place, unless something further is done to protect the joint from trauma.

In women suffering from this disturbance, where a high-heel shoe has been worn, lowering of the heel and increasing the thickness and the width of the sole lessens the strain thrown upon the metatarsal. A strip of leather or other firm material  $\frac{1}{8}$  inch thick (*metatarsal bar*), placed transversely across the sole just posterior to the distal ends of the metatarsals, will usually give complete relief, especially if the amount of walking or standing is restricted in some degree. Such a metatarsal bar was used in Case I, with prompt and complete relief of symptoms. The metatarsal bar

acts as a counter force to furnish support for the anterior part of the foot. Its form today varies considerably depending upon the desires of the orthopedic surgeon who has prescribed it. There is no standard shape or thickness that is suitable for every case. Perhaps the most generally useful shape is the type that is curved to correspond to the curve formed by the distal ends of the metatarsal bones. The bar is usually  $\frac{1}{8}$  to  $\frac{1}{4}$  inch thick but may be made thicker in one portion or another, depending upon the desires of the surgeon prescribing it.

### EPIPHYSITIS OF CALCANEI

*Case II.*—A. D., a male child aged eight years, was brought in by his mother with the explanation that the child had always had "flat feet," and that during the last nine weeks he had been limping and complaining of pain in both heels when walking about the house in his bare feet. He had always been perfectly comfortable when wearing his shoes. Examination revealed a moderate genu valgum and slight shortening of both Achilles tendons. The first metatarsal bone was loose and shorter than the second. The relationship of feet and legs was excellent, there being only a questionable degree of pronation. Inside the shoes were long stiff leather arch supports glued in place. The gait was normal at the time of examination and the appearance of the feet and their relationship to the legs was such that it made it difficult to believe that the painful heels arose from any disturbance in balance.

Five days later when this child returned for a second examination, the pain in his heels had become much worse and was then present whenever he walked. At this visit the child was able to point out with his finger the exact location of the pain, which was at the posterior inferior margin of the heels. At this point there was distinct tenderness on pressure on both heels. Lateral roentgenograms of the feet revealed definite ossification of the epiphyses of the calcanei, the left being much smaller than the right. Both epiphyses were rough, irregular, small and fragmented, but there was no variation in density.

In reviewing the *history* of this case with the mother, it was learned that she had been told by her pediatrician shortly after the child was born that it had "flat feet." No recommendations were made for management or periodic examinations. As a result of a conference with a shoe clerk, the mother had kept leather arch supports in this child's shoes ever since he first walked. Upon the advent of painful heels, the mother, believing the symptoms to be due to some manifestation of the "flat feet," decided to consult a physician for advice.

Frequently children in the first or second year of life are described as having flatfoot. This conclusion is often erroneously drawn from the flat appearance of the sole or from the footprint. The sole of the foot may appear flat as a result of the presence of soft tissue structures beneath the arch, and

by virtue of this same fact the footprint may be very broad, yet in either instance the arch may be well formed. Physicians should be very careful about the loose application of the term "flatfoot" when referring to the condition of the feet in children. Such a diagnosis often sends anxious parents scurrying here and there hunting for the talisman that will cure the "flatfoot" that never existed.

The little boy presented in this case was an extremely active child. He lived on the third floor of a building and made about twenty trips up and down stairs daily. Such activity certainly calls for a lot of work from the Achilles tendon and its related structures such as the Achilles bursae, the periosteum and the epiphysis of the os calcis. It was important in making the *diagnosis* in this case to consider several important conditions that might be responsible for the pain, such as irritation of the bursae in the region of the insertion of the Achilles tendon, inflammatory changes in the Achilles tendon arising out of strain or overuse, epiphysitis (apophysitis) and periostitis, as well as pain from overuse of a slightly pronated foot. *Bursitis* is characterized by tenderness and swelling in the region of the bursae just anterior or posterior to the Achilles tendon near its insertion. *Tenosynovitis* is characterized by tenderness and swelling over the lower portion of the Achilles tendon. In this case there were no specific symptoms of bursitis or tenosynovitis. Because of the age of the child, the history of excessive activity of the Achilles tendon, and the specific location of the tenderness and pain, a diagnosis of epiphyseal disturbance was made.

Neither the *pathology* nor the *etiology* of epiphysitis is clear. Trauma has been explained as one of the probable causative factors. That assumption is reasonable inasmuch as the epiphysis is the seat of insertion of the powerful Achilles tendon. The diagnosis of epiphysitis by roentgenography in the early stages of ossification of the epiphysis is not so simple as might be adduced from a number of textbooks. Irregularities in the early normal ossification of the epiphysis can be quite easily confused with genuine, early, pathologic changes.

Regardless of the exact nature of the lesions about the heel in young children appearing as the result of trauma, the basis of successful *treatment* in all is *rest*. Physical therapy and alterations of the shoes under such circumstances are of secondary importance. In this case the parents were directed to keep the child in bed off his feet. After two days the mother reported that the child had made no further com-

plaints. The rest period should be continued for one week to ten days and then if there is complete absence of symptoms of tenderness and pain the child may be allowed up a little each day with a felt pad  $\frac{1}{4}$  inch thick placed in the heel of the shoe to take some of the strain off the Achilles tendon. If more complete rest is indicated, as in cases of true epiphysitis, the foot may be immobilized in a plaster-of-paris cast extending from the toes to above the knee, with the foot in moderate equinus. After three weeks the knee may be mobilized by the removal of an upper section of the cast. The lower part of the cast extending from just below the knee to the toes should remain in place for another three weeks. Following the complete removal of the cast there should be a gradual return to weight-bearing, the heel being protected by a felt pad in the shoe or adhesive strapping about the heel.

#### METATARSOPHALANGEAL ARTHRITIS

*Case III.*—Mrs. S. G., aged forty-three, weight 146 lbs., height 5 feet, 4 $\frac{1}{4}$  inches, came for advice because of pain of three years' duration in the left great toe joint. The pain was confined to the first metatarsophalangeal joint, was present only on walking, and had become much worse the past three months. Lately she had noticed that there was a sore feeling in the region of this joint that persisted, especially after she had been on her feet a great deal. There was no history of injury.

Physical examination of the foot revealed tenderness on pressure about the superior aspect of the joint and large, palpable irregularities about the distal end of the first metatarsal. The roentgenogram revealed a narrowing of the joint space at the first metatarsophalangeal joint, together with exostoses about the head of the metatarsal.

This patient showed no arthritic manifestations or other symptoms of joint disturbance in any part of the body except the left foot. In disturbances such as this, arthritis, bursitis and gout must be differentiated. The patient with *gout* usually gives a history of periodic acute attacks of pain which have no relation to weight-bearing. In the more chronic state there is considerable enlargement about the joint that can hardly be confused with *bursitis* or the hypertrophic changes of *arthritis*. Arthritis in the great toe joint may be a part of a general arthritis or a local condition in the foot. It frequently occurs in the great toe joint. A diagnosis of hypertrophic arthritis was made in this case, based on the symptoms of pain brought on by use, limited motion and the x-ray findings.

The most effective treatment for a painful arthritic joint is *rest*. If the range of motion in the joint is permanently

restricted, then the resumption of use that requires extension of the great toe joint at every step is bound to produce a recurrence of the pain and disability following a rest period. Lowering the height of the heel where a high heel has been worn takes much of the strain off the joint and in itself may be all that is required to bring about a marked alleviation of the symptoms. This was the result in the case presented here. In other instances one may find it necessary to thicken the sole of the shoe by the insertion of a wedge in the sole beneath the great toe joint. In some cases this works perfectly, while in others it causes discomfort by shifting the weight too much to the outer side of the foot. A very effective method of bringing about relief is by the insertion between the inner and outer sole of a strong flexible piece of steel 1 inch wide and long enough to reach from the center of the heel to the front end of the shoe. This is most successful in the low heel shoe and brings about relief because it protects the joint of the big toe from excessive dorsal flexion. When conservative measures fail to bring about sufficient relief, surgical intervention becomes a necessity.

#### MARKED SHORTNESS OF THE FIRST AND FOURTH METATARSAL BONES

*Case IV.*—Mrs. E. B., aged fifty years, came in for treatment because of severe cramplike seizures in the region of the distal ends of the third and fourth metatarsals of the right foot. This disturbance had been present for one month and had manifested itself in the form of brief attacks that came on suddenly while walking. She mentioned that along with her pain there was a sensation in her foot of one bone cracking against another. She had had trouble with callosities on the ball of her foot for two to three years, but the distress from them was mild compared to her more recent attacks of pain. She was 5 feet in height and weighed 132 pounds.

On examination the patient's feet were seen to be markedly clawlike. Plantar flexion was greatly limited in all toes, but the limitation was most pronounced in the fourth and fifth toes. Inspection of the lower extremities in the standing position revealed a marked genu valgum. In this position the fourth and fifth toes did not come in contact with the floor. The first metatarsal segment was very loose. Inspection of the soles of the feet revealed a callosity  $\frac{1}{2}$  inch in diameter beneath the distal ends of the second metatarsals.

The patient's shoes gaped widely opposite the malleoli. The medial and lateral borders of her feet extended far over the borders of the soles of her shoes. The heels of her shoes were  $1\frac{3}{4}$  inches high. The roentgenogram of her right foot (Fig. 6) revealed a striking variation from the normal in the lengths of the metatarsal bones. The first was moderately shortened and the fourth was extremely shortened. Hyperthrophic changes were present at the lateral portion of the proximal end of the first metatarsal. The fourth metatarsal, in addition to being extremely short, showed unusual narrowing of the shaft and a lessened normal density at the distal end.

Shortness of the first metatarsal bone, as well as moderate variation in the forward projection of the other metatarsals, is a common occurrence. Extreme variations are not so common but may occur as congenital deformities or as disturbances in ossification representing a developmental defect. The short, loose first metatarsal segment and the short, inadequate fourth metatarsal have seriously interfered with the natural distribution of weight in this foot. Further evidence of this fact is demonstrated by the callosity beneath the distal end of the second metatarsal which projects the greatest distance



Fig. 6 (Case IV).—Roentgenogram of right foot, showing extreme shortness of metatarsal IV and moderate shortness of metatarsal I.

forward of all the metatarsals and thus carries an excess burden as the weight is thrown forward on the anterior part of the foot in walking. The hypermobility of first metatarsal segment and the hypertrophic changes at the proximal end of the first metatarsal can well explain the "cracking together" sensation described by the patient.

Morton in his book on the human foot explained the pain occurring in the third and fourth toes as due to irritation of the median plantar nerve by synovitis occurring at the proximal end of the second metatarsal when that bone has excessive weight thrown upon it. The shoe in this case, with its

high heel and extremely narrow sole, has been a very definite factor in bringing about the production of symptoms. In the first place, the raised heel throws more than a natural share of the weight continuously forward on the anterior part of the foot; and this part of the foot, defective to begin with, must carry this extra burden and carry it on a surface that is much too narrow, thus allowing a still greater burden to be thrust forward on an already overloaded second metatarsal.

Armed with a thorough understanding of the production of the pain or discomfort in this case, the *treatment* is obvious. A low, broad, stable heel not more than  $1\frac{1}{4}$  inches high and a broad, thick though flexible sole (wide enough for all five metatarsals) are the essential requirements for the shoe.

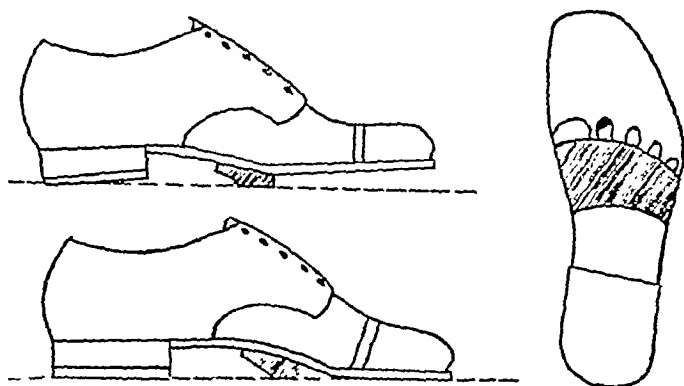


Fig. 7.—Metatarsal bar and its effect on the shank of the shoe when weight is borne upon the foot.

When the patient described here was supplied with such a pair of shoes her symptoms were at once alleviated. Under such circumstances she has now been comfortable for three years.

When there is a recurrence of symptoms after a suitable shoe has been supplied in the presence of an extreme variation in the lengths of the metatarsals, it may become necessary to place a piece of properly shaped leather or hard felt inside the shoe beneath the shortened metatarsals in order to relieve the strain on them. However, a metatarsal bar or strip of leather placed on the sole of the shoe just posterior to the heads of the metatarsals often is more effective, and it does not take up space in the shoe as do the pads placed inside.

A review of the medical literature on the effects of marked



shortness of the first metatarsal reveals that in such cases the weight, when thrown forward on the anterior part of the foot, is excessive on the adjacent second metatarsal. There is a certain natural distribution of the weight over the metatarsal bones when the normal foot is in use in locomotion. When one of the metatarsals is unnaturally short it cannot possibly carry its allotment of weight and as a result its share of the burden is thrown upon the adjacent metatarsals.

Whenever pain is present in the anterior part of the foot in the region of the anterior ends of the metatarsals, one must aim his attention at a study of the anatomy of this part of the foot as well as at the proportionate load it is carrying. In walking, the weight streams forward from the heel through the tarsal bones and over the metatarsals, half of it passing over the first and second metatarsal bones. Often the first metatarsal bone is short, and then the long, projecting second metatarsal bears the bulk of the burden. In addition to being short, the first metatarsal segment is sometimes loose, thus interfering seriously with the stability of the median side of the foot. In such cases the bulk of the strain goes to the second metatarsal. This variation in the first metatarsal alters the distribution of the weight over the front part of the foot. In the presence of such anatomic variations, symptoms are brought about from excessive use, from the extra total burden of the obese individual, from the undue proportion of the natural weight thrown constantly forward on the anterior part of the foot when high-heel shoes are worn, and from inflammatory changes following the long-continued strain on the metatarsophalangeal joints.

#### NEGLECTED SPRAIN, EXCESSIVE WEIGHT AND A FAULTY SHOE

*Case V.*—Mrs. G. G., aged fifty-four, school teacher, came for treatment because of pain near the astragaloscaphoid joint for ten months, pain in the left popliteal region, and swelling of the left foot. Her trouble began with an acute sprain of the left foot which occurred ten months prior to her arrival for treatment. She related that her left foot had been sore ever since the day she had sprained it. It became swollen and painful after walking or standing. There was little improvement since the onset of symptoms ten months before. She had received no treatment for the original sprain.

This patient was 5 feet 5 inches tall and weighed 170 pounds. There was a point of tenderness on the sole of the left foot. Her second to fifth toes showed sharp ridges from compression in her shoes. She had two devitalized teeth. The roentgenogram of her left foot showed an accessory scaphoid bone and some very slight hypertrophic changes at the distal end of the first metatarsal and at the proximal margin of the navicular bone. Her shoe was a wide-strapped suede slipper type, old and worn, with a small heel 2 inches high.

This case is reported because it demonstrates several very important points, namely a neglected sprain, a question of arthritis in the presence of focal infection, excessive weight and a faulty shoe.

The findings in this case suggested arthritis, aggravated or initiated by trauma. The prolongation or continuation of the symptoms was due to neglect of a sprain, obesity, and a wobbly, flimsy, unstable shoe. The trend in the treatment of mild sprains today is toward initial rest and local treatment fol-

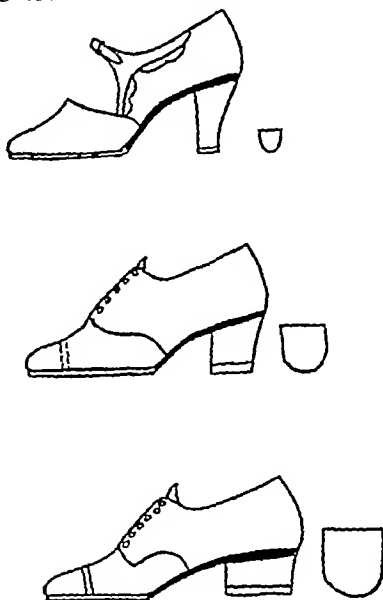


Fig. 8.—All three of the shoes shown are the same shoe-size. Note the marked difference in the size of the inferior surfaces of the heels as depicted by the small figure to the right of each shoe. The uppermost shoe (the type worn in Case V) with its high slender heel affords little stability and increases the strain on the anterior part of the foot.

lowed by early active use with sufficient support to protect the affected structures. This woman had no initial rest or local treatment and no support. Instead, she subjected the injured foot to the same excessive duty of carrying 170 pounds and she continued to wear a shoe that lacked the most important elements, support and stability. In the presence of swelling and pain she carried on for ten months, until the symptoms became so severe that the possibility of having to give up her occupation began to loom up prominently.

Disregarding the sprain, the symptoms here are those experienced by thousands of persons suffering from foot disturbances in middle life. In such persons the foot is in middle life, too, but little consideration is given to that fact by anyone until the advent of symptoms which compel attention. Individuals who have hitherto been practically free from foot disturbances begin to have trouble because of excessive weight at a time when the burden should be lighter rather than heavier and also because the foot is required to function in a form of wearing apparel that neither affords enough room for the foot nor permits a fair and sensible distribution of weight. The etiologic factors in these cases are *age, weight* and *shoes*.

These factors must be kept well in mind in the choice of *treatment*. Rest is prescribed, and an attempt is made to reduce the body weight. The distribution of weight over the foot is improved by ordering a suitable shoe.

The patient portrayed in this case was directed to eradicate foci of infection such as the devitalized teeth, to reduce weight, to obtain a more natural distribution of the weight on the foot by wearing satisfactory shoes during working hours, and to take sufficient daily rest off the feet. She was co-operative, carried out the recommendations and within three weeks she had shown marked improvement. Her comments were that she felt much better, but she didn't know for sure whether her improvement was due to the extraction of the teeth or to the new shoes.

#### CONGENITAL DEFORMITY OF FIFTH TOES

*Case VI.*—P. S., a nine-year-old boy, was brought for treatment because of a deformity of both fifth toes. The condition had been present since birth. Inspection showed the fifth toe in an almost transverse position overlapping the fourth toe of each foot. There was no complaint of pain in this case, but the parents were concerned because the superior position of the toe caused it to rub against the shoe.

*Treatment* for such a condition as this should be begun shortly after birth. The attending obstetrician who manages the delivery of a child with a congenital deformity of this type should always apprise the parents of the necessity of instituting treatment in the first weeks of life. When treatment is delayed it becomes difficult or impossible to correct the deformity without resort to surgery. When one sees this type of toe in adults, the first expedient considered is usually *amputation*, since the toe is absolutely useless. Such a procedure may seem safe and simple, but the thought of amputa-

tion of even a small useless fifth toe causes some patients to retract in horror. L. A. Lantzounis described a *plastic operation* on the capsule and periosteum at the metatarsophalangeal joint for the correction of this deformity. Such a procedure certainly merits trial in preference to amputation. A simple plastic operation on the capsule of the metatarsophalangeal joint may suffice to maintain correction of the deformity.

### SPREADING FOOT WITH ARTHRITIS

*Case VII.*—Mrs. E. G., aged fifty-three, a housewife, came for relief because of pain under the ball of the foot of two years' duration, hammer toes for one year, bunions for ten years and a feeling of spreading between the toes for one month.

Examination revealed a spread-out foot excessively wide at the anterior region, with marked bilateral hallux valgus deformity. Sharp ridges were present at the margins of the toes. Both second toes were of the hammer type. Corns were present on the dorsum of the third, fourth and fifth toes of the left foot and on the second toe of the right foot. Callosities were present on the medial inferior border of both great toes and on the soles of the feet under the distal ends of the second metatarsals.

The patient wore moderately pointed Oxfords, the heels of which were  $1\frac{3}{4}$  inches high, with ground-contact area of less than 2 square inches. Inside the shoes she had heavy steel arch supports which she had been wearing for the past year. Roentgenograms of the feet revealed definite productive (hypertrophic) changes about both ends of the first metatarsals, with very wide-spreading or fanned-out metatarsals. This woman weighed 153 pounds and was 5 feet 5 inches tall.

Here is a woman of middle life, a little overweight, who has had discomfort in the anterior part of the foot for at least two years. Her foot is of a spreading type and hypertrophic changes are plainly seen in the roentgenogram. There are certainly two things that can be responsible for the pain, namely the excess burden on the anterior part of a spreading type foot and the arthritis. The callosities are the confirmatory signs of unnatural distribution of weight. The ridges on the toes represent the results of excessive lateral pressure from a too narrow anterior shoe compartment, along with an overly high heel that causes the foot to be forced down into the front of the shoe. It is true that this woman has bilateral hammer toe and hallux valgus deformities, but in the consideration of *treatment* these are secondary elements. Many such patients as this present themselves with their minds made up for an operation on the bunions and hammer toes, believing that only such measures will bring about relief. The better one is acquainted with the complicated etiology of hallux valgus, the less he will resort to surgery as an initial step when relief from

symptoms is the aim. After a little experience at securing relief by the use of simple fundamental conservative measures for patients with feet such as those described in this case, one begins to wonder if the cosmetic element has not been the biggest influencing factor on the decision to operate. In the many similar cases I have seen, failures in obtaining relief were few and far between when attention was given to the arthritis and to the establishment of a more natural distribution of the weight on the foot.

In this particular instance the treatment recommended was daily rest periods from 9 to 11 A. M. and from 2 to 4 P. M., during which the patient was directed to be off her feet. Contrast baths or whirlpool baths were ordered daily. The patient was provided with shoes having big, broad heels  $1\frac{1}{4}$  inches high and soles of a width that gave weight-bearing room to all metatarsals. The anterior compartment of the shoes was high enough to clear the toes and roomy enough to eliminate all squeezing. The shanks of the shoes were rigid but the front part of the soles was thick and flexible. The steel arch supports were discontinued.

When the patient returned for a check-up three weeks later she reported that she had been very, very comfortable. Two weeks later at the second check-up she complained of tingling in the toes; this was attributed to the tight elastic band she had just recently placed about the insteps of her feet. At this conference she was provided with metatarsal bars  $\frac{1}{8}$  inch thick on the soles of the shoes. After a few days she reported that since the application of the metatarsal bars she had had prompt and complete relief from the last vestige of pain under the ball of the foot, including the tingling in the toes. Exactly one year later the patient returned because of an acute ankle sprain. At this time she reported that she had been very comfortable all through the year.

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## CLINIC OF DR. J. P. GREENHILL

### COOK COUNTY HOSPITAL

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#### CONTROL OF PAIN IN CASES OF CANCER

GENTLEMEN, the ten men and women you have just seen are very unfortunate individuals. All of them will die within a year or two from cancer. In spite of this fact, the five who sat on the right side of the room appeared to be fairly cheerful and in good health. On the other hand, the five who sat on the left side of the room looked definitely unhappy, were in evident pain, and were emaciated. Why was there such a difference between these two groups of doomed men and women? The answer is simply that the happy-looking individuals had excruciating pain but were recently given complete or almost complete relief of their pain. As soon as their suffering subsided their appetites improved, they have been sleeping better and they naturally have a better outlook on life. The sad, suffering individuals on the left side have not yet been relieved of their more or less constant, agonizing pain.

Nearly all men and women who have inoperable carcinoma or a malignant condition which is too far advanced to yield to radiation therapy, sooner or later develop fairly constant, torturing pain. In some cases intensive radiation will relieve the pain temporarily, but after a while some special form of treatment must be given for the control of the pain.

First we should ask ourselves *why* these unfortunate patients invariably suffer from pain if they live long enough. The answer is simply that almost any malignant process, as it grows and invades surrounding tissue, soon involves sensory nerves. Irritation of these nerves produces pain. Since this irritation is present day and night, the pain is more or less constant. Those of you who have seen patients who suffer with pain from carcinoma know how pitiable these creatures are and what a burden and trial they are to their families. The only humane thing for us to do as physicians is give as much relief to these tortured individuals as possible. The

most difficult group to relieve are those, both male and female, who suffer from cancer of the pelvic organs.

The second question we should ask is, can we give relief from excruciating pain which is constant? The answer is decidedly yes. At the present time there are at least five fairly satisfactory ways in which pain can be relieved or prevented in cases of cancer. These are: (1) the use of *opiates*, (2) the administration of *cobra venom*, (3) intraspinal injection of *alcohol*, (4) *sympathectomy* and (5) *cordotomy*.

#### OPIATES

The simplest and most widely used method of relieving severe pain is to administer *morphine*, *pantopon*, *codeine*, *dilaudid* or other opium derivative. These drugs are helpful for a while in all cases but sooner or later they become unsatisfactory. The reasons for their inadequacy are: (a) The patient's tolerance for the drugs increases enormously so that larger and larger doses must be given. This means a constant increase in cost of the drugs, until poor people cannot afford them. (b) In some individuals the drugs produce nausea and vomiting. (c) A few men and women become drug addicts and are then difficult to handle.

Stroud<sup>1</sup> finds that in his experience *dilaudid* is more helpful in cancer than any other opiate. In order to obtain continuous relief of constant pain, the method of its administration is important. *Dilaudid* is rather rapidly absorbed and is quickly effective if given either by mouth or by hypodermic injection. Absorption is delayed when it is given by rectal suppository and consequently the action is more sustained. This is of distinct advantage in the administration of the bedtime dose. A simple dose gives relief for about three and one-half hours when given either hypodermically or by mouth. Hence, the best effects are obtained when the drug is given about every three hours. At bedtime the dose is doubled and given by suppository.

#### COBRA VENOM

The first impetus to the use of cobra venom was given by Monaelesser, but Macht<sup>2</sup> deserves the credit for constantly calling attention to this substance as an analgesic. Macht's experiments have proved that cobra venom, like opium and its principal alkaloid, morphine, relieves pain through its action on the higher centers of the brain. Hence, cobra venom like morphine may be given to relieve pain regardless of where

it is located in the body. The two drugs exhibit a marked difference, however, with regard to the time element involved in their pharmacologic action. Whereas morphine relieves pain very promptly, its effect wears off in a few hours. Cobra venom, on the other hand, does not induce analgesia rapidly. It is usually necessary to give an injection of the drug on each of several successive days before the analgesic action is fully developed. The relief of pain effected by cobra venom, however, once it is induced, lasts much longer than that of morphine. Furthermore, the opium derivatives depress mental performance, whereas cobra venom definitely stimulates mental activity.

The therapeutic doses of cobra venom produce no local anesthetic action either on the sensory or the motor nerve endings, or on the nerve fibers of the ascending or descending peripheral nervous system.

The *dose* usually recommended is 5 mouse units, although Macht in a personal communication recently wrote me that he is going to recommend doses of 10 mouse units as the average therapeutic dose. One mouse unit is the quantity of cobra venom solution required to kill a white mouse weighing 22 gm. within eighteen hours after intraperitoneal injection of the drug.

It is best to begin with half the contents of an ampule, or  $2\frac{1}{2}$  mouse units. On the following day a whole cubic centimeter (5 mouse units) is injected. Similar doses of 5 or 10 mouse units each are injected for several successive days until a definite analgesia is noted or a contraindication for the use of the drug is encountered. The latter is rare. Usually relief from pain is observed from the third to the seventh day after the beginning of the injections. If the patient does not respond after seven days, there is little likelihood that cobra venom will be of any help.

Once analgesia has been established, the patient may usually be kept comfortable with two or three injections of 5 mouse units each week. This may be continued for many months. The injections are given intramuscularly. There are very few local reactions such as infiltration and pain.

In Macht's series of 185 patients, most of whom had cancer, 70 per cent showed definite relief of pain and 10 per cent more had slight relief.

Parenthetically I may tell you that cobra venom sometimes relieves the pain which is associated with severe roentgen ray and radium burns.



Cobra venom is not expensive and it may be administered by the patient himself. There is no danger of habit formation, of increased tolerance or of toxicity of the drug, hence I would advise you to try cobra venom in some cases of hopeless malignancy associated with severe pain. One of the five treated patients whom you saw a little while ago was relieved of his pain by cobra venom.

#### INTRASPINAL INJECTIONS OF ALCOHOL

A simple procedure used to relieve pain in a large group of cancer patients is the intraspinal (subarachnoid) injection of alcohol. This form of treatment was suggested by Dogliotti<sup>3</sup> in 1930 and is based on Lugaro's contention that the sensation of pain may be removed by a simple reduction in the number of peripheral sensory nerve fibers. For the purpose of decimating the peripheral nerve fibers in the posterior or sensory roots of the spinal cord, Dogliotti chose the subarachnoid space. Injection of alcohol in this region will prevent painful peripheral stimuli from reaching the medullary centers, even if the stimuli act at the level of the spinal ganglions, the intervertebral foramina or the spinal roots.

I<sup>4, 5</sup> began using intraspinal injections of alcohol for excruciating pain associated with malignancy in the female pelvis in 1934. In a series of well over 100 cases of Group III and Group IV carcinoma of the cervix, which is the most common cancer in women, complete relief has been obtained in about 75 per cent of the cases and partial relief in about 10 per cent more. The relief usually lasts many months—in many cases until the patient dies from his or her cancer. The only patients with inoperable carcinoma of the cervix who are not suitable candidates for intraspinal alcohol injections are those who have pain in the kidney region and in the parametrium due to stricture of the ureter associated with hydro-ureter and hydronephrosis. The technic of intraspinal (subarachnoid) injection of alcohol is simple, and it is quickly performed and with little discomfort. However, since there is a possibility that, in some cases, the spinal cord may be injured, this procedure should be used only for men and women who have cancer.

The *technic* of the injection in cases of pelvic malignancy is as follows: No preliminary medication is given because we wish to observe the immediate effects of the injection. Most patients with advanced carcinoma of the pelvic organs have much more pain on one side than on the other. The patient

is placed on the side opposite to that where most of the pain is present. A pillow or pad is placed under the pelvis and side to elevate the sacral and lumbar portions of the spine, the back is arched as much as possible, the body is turned somewhat ventrally, and the head is lowered slightly. By placing the patient in this attitude we raise the sacrolumbar region of the spine to the highest level and at the same time make the posterior or sensory nerve roots lie horizontally. The anterior or motor nerve roots come to lie in a plane which is usually out of reach of the alcohol. Even if the motor nerves are not removed from the field of the alcohol, as occurs in the cauda equina, they are not often affected because sensory nerves are more susceptible than motor fibers to the effects of alcohol.

Someone should hold the patient in the proper position. A weak solution of iodine or other antiseptic is applied over the lumbar and upper sacral regions. Injection is made in the second, third or (usually) fourth lumbar interspace. An ordinary lumbar puncture needle with a stylet is used. The needle is inserted into the desired interspace just as for an ordinary lumbar puncture, and novocain is injected into the skin before inserting the needle. After the needle is in the sub-arachnoid space, as evidenced by the flow of spinal fluid, 0.75 cc. of absolute or 95 per cent alcohol is injected into the cerebrospinal fluid. For this purpose it is best to use a tuberculin syringe in order to make sure that not more than 0.75 cc. of the solution is injected. Furthermore, the alcohol must be injected very slowly, drop by drop, allowing about two minutes for the injection of the 0.75 cc. The alcohol rises immediately to surround the posterior roots because the specific gravity of alcohol is about 0.806, whereas that of the spinal fluid is 1.007 to 1.011. No attempt should be made to draw spinal fluid into the syringe to mix it with the alcohol; in fact, this is exactly what is not wanted. After the injection is made the needle is withdrawn and the puncture hole is covered with sterile gauze and adhesive.

Before the injection is completed, the patient will complain that the upper leg feels numb or hot, and that the leg cannot be moved. The numbness is almost routinely experienced after the injection but disappears spontaneously after a few hours or few days in most instances. In spite of what the patient says concerning inability to move the leg, when he is requested to move it he will meet no difficulty. At the time the patient informs us of the numbness he also often tells us, either voluntarily or in answer to our query, that the pain has

disappeared. The longer the patient is permitted to lie on the side, the better the results. Hence, the patient should be kept on the side for two hours after the injection, after which period he is permitted to get up and walk around. Sometimes

TABULATION  
OUTLINE FOR REGIONAL ALCOHOLIC PAIN BLOCKING\*

Organ involved.		Type of block.	Site of injection.
Head		Trigeminal block	I, II, III divisions: (a) Terminal nerves (b) Subganglionic block (c) Gasserian ganglion block
		Stellate ganglion sympathetic block	(a) Paravertebral, between first and second ribs (b) Subarachnoid T 1-2. Especially important in connection with trigeminal pain or neuralgia
Neck		Cervical plexus block	Paravertebral
Upper extremity		Subarachnoid block	T 2-3 Exceptional, T 1-2
Chest	Larynx Trachea Bronchi Lungs Heart†	Subarachnoid block	T 3-4
	Aorta† Esophagus†		Upper part T 3-4 Lower part T 8-9
	Pleura		Entire T 6-7 or T 7-8 Upper part T 3-4 Lower part T 8-9
Abdomen	Aorta† Spleen	Subarachnoid block	T 5-6
	Stomach† Liver† Pancreas† Small intestine†		T 6-7 or T 7-8
	Colon†		T 11-12 or T 12-L 1 Ascending and transverse colon T 4-5
	Kidney-suprarenal gland		T 11-12
Pelvis	Ovaries Testicles Uterus Tubes Ureters Seminal vesicles Prostate† Urethra† Bladder†	Subarachnoid block	T 12-L 1 and L 4-5
	Rectum—anus		L 4-5
Lower extremity		Subarachnoid block	T 11-12 (Sympathetic) and L 1-2 (somatic)

\* In blocking the long viscera, aorta, small and large intestines, or in special cases, it may be necessary to repeat the block one or several segments higher or lower than the levels given above. This outline applies only to the adult body.

† Lesions affecting these organs usually involve the sympathetic nerves of both sides. Bilateral (right and left) injections should be given in these cases.

a patient finds difficulty in getting up from a chair because his "leg is asleep." In other instances the leg feels heavy and the patient experiences some trouble in walking up steps because the knee flexes readily. These sensations usually wear off in a few hours, although in some patients they last a number of weeks.

Nearly all of the patients who are ambulatory may be permitted to go home within three hours after the injection. No ill effects will be observed from this procedure. It is perhaps best, however, to keep a patient in a hospital for twenty-four hours after an injection. I should like to emphasize that the intraspinal injection of alcohol may easily be carried out in a patient's home. This is important to remember because many individuals with cancer are bedridden at home and there is no need to subject them to the inconveniences and expense of transportation to a physician's office or a hospital.

If the patient has pain on *both* sides, an injection is made a week later with the patient lying on the opposite side. The same amount of alcohol is injected.

The *site of injection* depends upon the organ or organs which are involved. The accompanying tabulation is adapted from an excellent article on this subject by Stern.<sup>6</sup>

Three of the cheerful patients you saw this morning had been dramatically relieved of their pain by means of intraspinal alcohol injections.

#### SYMPATHECTOMY

The operation known as sympathectomy or neurectomy consists in the removal of portions of the sympathetic nervous system in order to interrupt the pathway of pain sensation. There is no harm in removing segments of this part of the nervous system. It is of course a much more extensive procedure than intraspinal alcohol injection because it usually requires a laparotomy and a fair amount of manipulation. In cases of pelvic malignancy the operation will yield almost perfect results if it is restricted to patients who have pain in the middle of the lower abdomen, pain low in the back, rectal tenesmus, pain in the bladder and pain associated with vesicovaginal and rectovaginal fistulas. The operation is useless, however, for patients in whom the pain is due to compression of motor nerve roots by carcinoma, or involved lymph nodes or pain due to distant metastases.

The *technic* of pelvic sympathectomy which I<sup>7</sup> use is as follows: Since many of the patients who should be subjected

to this type of operation are poor surgical risks, it is best to open the abdomen under direct infiltration anesthesia. This is a very simple procedure and requires only a few minutes. The rest of the operation may readily be performed under a short ethylene or vinethene anesthesia or even under infiltration anesthesia. The patient is placed in the Trendelenburg position after a midline incision has been made from the umbilicus downward toward the pubis for from 10 to 12 cm. After the peritoneal cavity is opened, the small intestine is packed off and the sigmoid and rectum are pushed to the left side and held there with a wide retractor. The region of the lower two lumbar vertebrae and the upper part of the sacrum is exposed to view. In thin individuals, it is possible in some cases to see the presacral nerve immediately beneath the peritoneum. Whether or not the nerve is seen, the parietal peritoneum above and in the middle of the sacral promontory is elevated and incised with scissors. This incision is extended upward for about 4 or 5 cm. and for a similar distance down along the sacrum. When the peritoneal flaps are pulled aside, a fibrocellular connective tissue layer will be exposed, covered by more or less adipose tissue. This tissue can easily be separated from the peritoneum and the lower end of the aorta without danger. It is in this layer that the presacral nerve lies. With an aneurysm needle the tissue is elevated at the bifurcation of the aorta and the dissection is carried to a still higher level. As this is done, it will be found that in most instances the tissue spreads out triangularly. The middle sacral artery should be pushed away from the nerve, but if it is injured it can readily be ligated.

After the dissection is carried as high as it is desirable to go, the layer of nerve tissue is separated from the underlying tissue down past the sacral promontory into the pelvic cavity. In this region the plexus has divided into two hypogastric nerves; hence it is necessary to dissect one of these nerves at a time. At least 2 or 3 cm. of each hypogastric nerve should be resected in addition to 4 or more centimeters of the superior hypogastric and the intermesenteric plexuses. The fibrous tissue layer, which contains the hypogastric nerves, is much more resistant than that which contains the presacral nerve. As the dissection is carried out, nerve filaments projecting outward will be encountered. These should be followed as far laterally as possible before they are cut. In most instances, ganglions will be included in the resection. The dissected tissue should preferably be removed in one piece. It is not necessary or

advisable to ligate the presacral nerve or the hypogastric nerves before cutting them, because the only blood vessels in intimate contact with them are insignificant vasa nervorum. Very rarely does one encounter bleeding that requires more than simple temporary pressure to check it. (When the mesosigmoid is very short, care must be exercised to avoid injury to the inferior mesenteric vessels.) After the nerve is resected, the posterior parietal peritoneum is sutured with plain catgut and the abdominal wall is closed in the customary way. Since the patients with inoperable carcinomas are usually cachectic and exhibit poor wound healing, it is advisable to use silkworm gut or other permanent suture material to aid in the closure of the abdominal wall in such cases.

One of the relieved patients you saw this morning had undergone pelvic sympathectomy.

#### CORDOTOMY

In 1904 Spiller<sup>8</sup> arrived at the conclusion that pain-conducting fibers from the extremities and the trunk pass upward to the brain in the spinal cord by way of the anterolateral columns. In 1912 this contention was verified by Martin<sup>9</sup> who sectioned the anterolateral spinal tracts and thereby completely abolished the appreciation of painful stimuli in all the skin segments below the point of section. Frazier<sup>10</sup> developed the technic of cordotomy as it is generally practiced today.

Pain in any area below the ensiform, regardless of whether it is unilateral or bilateral, can be relieved by cordotomy. According to Grant,<sup>11</sup> this operation has three distinct *advantages* over other methods of relieving pain. First, since in the anterolateral columns of the spinal cord the pain fibers are compactly collected, a section there produces the largest possible area of anesthesia. Secondly, pain and temperature sensations alone are obliterated without involvement of touch or position sense, and hence the usefulness of the lower limbs is not impaired. Lastly, the operation requires only a small laminectomy and is therefore much less exhausting than other operations. However, cordotomy has the *disadvantage* that unless the incision in the cord is accurately placed, the pain may not be completely relieved or the motor pathways may be damaged, resulting in paralysis of the legs and interference with sphincter control. Another disadvantage is that this operation must be performed only by a neurosurgeon or a general surgeon who has had considerable experience.

By the combined use of gas and oxygen anesthesia, with

novocain, one may cut the pain tracts under local anesthesia and determine with accuracy the level of loss of pain sensation by sensory tests carried out during the operation. The *point of election* for performing cordotomy is the fourth thoracic spinal segment, lying beneath the tip of the second and the body of the third thoracic vertebrae. At this level the cord is readily accessible. Grant<sup>11</sup> performed cordotomy in twenty-five cases of the pelvic type and obtained complete relief in twenty-one cases and partial relief in four. The mortality was 10 per cent.

Grant's *technic* is as follows:

"The day before the operation is to be performed, the patient is placed in the prone position and is rehearsed in the tests for pain sensation, especial emphasis being placed upon the differentiation between pain and touch. The surgical procedure consists in the removal of the appropriate lamina under gas oxygen anesthesia and novocain infiltration. The bony edge of the vertebral canal on the side of the tract section should be cut well back for easier manipulation of the cord. The dura is opened and the point selected at which the anterolateral column is to be incised. A dentate ligament is grasped in a mosquito hemostat and the cord rotated posterolaterally. If a posterior root crosses the field, it is ligated, cut and retracted. The wound edges are now carefully packed with sheets of cottonoid saturated in  $\frac{1}{2}$  per cent novocain. By this means perfect local anesthesia is obtained and the patient's attention is not distracted from the subsequent tests by pain in the operative field. The gas oxygen anesthesia is now stopped. The lower extremity upon the side to which the pain is referred is exposed for the testing of sensation. Time is allowed for the patient to recover entirely from the anesthesia, until replies to tests for pain sensation in the legs and feet are prompt and accurate. The cord is now rotated by traction on the dentate ligament and a very superficial incision made, barely sufficient to cut the pia, from just anterior to the attachment of the dentate forward to the lip of the anterior median fissure. Section of the pain tracts in the cord is not productive of pain stimuli, and may be done upon the conscious patient without causing distress.

"After this initial incision has been made, loss of pain sensation in the limb is determined. Usually after this first shallow section, pain stimuli about the foot and ankle are abolished. The incision is now deepened, care being taken never to extend it posteriorly beyond the attachment of the dentate ligament. With each increase in the depth of the section, sensation is tested. The level of anesthesia to pain can be raised from the ankle to the knee, to mid thigh, to Poupart's ligament, to the iliac crest, to the umbilicus and if necessary to the ensiform. But if the pain is referred to the perineum and down the leg, it is not necessary to push the sensory loss above the iliac crest. In this way, just sufficient pain fibers are cut to affect the necessary relief and little or no chance is taken of damaging the pyramidal tract. Furthermore, the muscular power of the leg upon the same side as the incision into the cord may readily be tested to determine whether or not motor pathways are being involved.

"If the distribution of the pain indicates the necessity for a bilateral cordotomy, precisely the same procedure is carried out on both sides of the cord. It is important, however, not to cut both anterolateral tracts at the same level.

One incision should be two segments above or below the other. After cordotomy has been performed, the wound may be closed under local or gas oxygen as occasion demands."

#### OTHER MEANS OF RELIEVING THE PAIN OF CANCER

Undoubtedly you all have read about Fay's use of *refrigeration* for the control of pain in cancer cases, since lay magazines and newspapers recently devoted considerable space to this revolutionary form of treatment. Fay and Henny<sup>12</sup> devised special apparatus to modify the local temperature in and about the area of carcinoma, over extended periods of time. They found that following local refrigeration there was prompt and gratifying relief of pain. Likewise, there was improvement in the patient's general physical state with gain in weight. This method is particularly advocated for the *hopeless* and *far advanced* cases of metastatic malignancy where pain is a prominent symptom.

Smith and Fay<sup>13</sup> more recently treated patients afflicted with hopeless and terminal stages of malignancy who presented themselves for relief of pain by *hibernation*. These authors subjected patients to reductions of body temperature ranging from 74° to 90° F. Previously it was believed that prolonged reduction of temperature below 94° or 95° F. was inevitably fatal. However, Fay and Smith maintained patients for from five to eight days at temperature levels in the 80's and found that this treatment brought about relief of pain for periods varying from a few days to five months. Furthermore, regressive changes in young embryonal cells, particularly in carcinoma, took place as a result of the therapy. The authors believe that the lowered physiologic activity due to the low temperature interferes with the metabolism of these cells. Gerster<sup>14</sup> and his associates investigated the "artificial hibernation treatment" or "cryotherapy," and found that in eleven out of seventeen cases of intractable pain due to carcinoma, there was sufficient alleviation of pain to obviate the necessity of administering narcotics for variable periods. Eventually pain recurred in all cases, in some as early as twenty-four hours after treatments were discontinued. This form of treatment is entirely too new to pass any judgment on it. We must also remember that refrigeration is not devoid of risk.

Another method advocated by Thurz<sup>15</sup> for the relief of pain in incurable cancer is the *intravenous injection* of a 33 per cent *ethyl alcohol* solution. This is made of one part alco-



hol and two parts physiologic saline solution. One cc. per kilo (2.2 lbs.) is given every third day. The solution must be administered slowly, 30 to 40 drops per minute. The total amount given is increased as the patient's tolerance increases, until it reaches between 400 and 600 cc. at one time. A small amount of saline solution must be injected before the alcohol is used and also to wash out the needle before it is withdrawn. This is to avoid pain and damage to the skin by the alcohol. Thurz believes the alcohol has a direct effect on the cancer.

In some cases *radiation therapy* in the form of deep roentgen ray treatment or radium will definitely relieve the pain of cancer. However, most of the patients who have persistent pain due to carcinoma have already been given all the radiation therapy they dare receive.

Behan<sup>16</sup> recommended the use of *calcium gluconate* intravenously, intramuscularly and by mouth to relieve the pain of cancer. The dose by mouth is 2 gm. three times a day. Cod liver oil, one teaspoonful three times a day, should be given to stimulate the activity of the calcium. The latter acts directly on the sensory receptors and thus reduces pain.

In conclusion may I urge all of you to give some thought to the problem of relieving pain of cancer. Victims of incurable cancer have a sad enough time waiting for death to relieve them. As physicians we must do all in our power to prevent these unfortunate individuals from being tortured physically as well as mentally.

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## CLINIC OF DR. WALTER W. HAMBURGER

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### THE TREATMENT OF HYPERTENSION

TREATMENT is always a difficult matter to write or talk about. It involves not only the science but the art of medicine. It is a most individual and personal problem, both from the patient's and physician's viewpoint. It must be predicated on accurate diagnosis, which in turn is the result of careful, painstaking study and analysis. It must be modern and abreast of the times, at the same time encompassing all the important valid methods and measures of the accumulated wisdom of our predecessors. It should be individualized to fit the particular patient, not only the disease from which he suffers. It must be elastic and resourceful, as the clinical and individual problem varies from hour to hour and from day to day. It should be directed to an attempt to modify the underlying disease process as well as the distressing symptoms and subjective complaints; it should encompass the patient's whole mental and emotional state and his reaction to his own illness. It involves the "handling" of the patient's family, friends, and business associates, and often giving advice concerning familial, economic and social problems: truly a task of major difficulty and importance but one well worth doing!

In this clinic I propose to discuss very briefly a few of the more outstanding historical milestones in our present-day concept of arterial hypertension; experimental hypertension; classification; the treatment of hypertension in general and its more important complications; and present a few representative clinical cases illustrative of some of the more usual types of hypertension met with in daily medical practice.

#### HISTORICAL

Richard Bright (1827), noting the increased resistance which the arteries of diseased kidneys offered to injection, is generally credited with being the first to appreciate the relationship of cardiac hypertrophy to renal conditions and pos-

sibly to arterial hypertension (Fishberg). Toynbee (1846) "showed that in the contracted kidney, the small arteries were thickened and narrowed, thereby accounting for the difficulty that Bright encountered in injecting such organs" (Fishberg). In 1858 Johnson found that thickening of the small arteries in Bright's disease is not confined to the kidney, but is also present in the arterioles of other organs, a finding which Keith has in recent years abundantly confirmed. Huchard and Allbutt advanced the theory that hypertension due to generalized vasoconstriction is the primary manifestation and the organic vascular disease a consequence of this condition (Goldblatt). The Heidelberg clinician, Ludolf Krehl (1913), insisted on the importance of disease of the blood vessels generally as the cause of increased blood pressure, while the German pathologist Fahr (1914), emphasized the importance of these arteriosclerotic vascular changes in the renal arteries themselves.

I recall vividly the great Huchard of Paris, at the International Congress at Budapest in the late summer of 1909, speaking on the cause of arteriosclerosis. Romberg of Tübingen, Schlesinger of Vienna, Koranyi of Budapest, Thayer of Baltimore and many others participated. As a young graduate medical student I had the privilege of listening in, while presenting a résumé of my own work on atherosclerosis of the gastric vessels. Romberg's discussion of Huchard's paper was particularly enlightening. For the most part they were in accord, both emphasizing that hypertension was the precursor of arteriosclerosis. Romberg, however, pointed out the frequency of arteriosclerosis with normal or low pressures, concluding that hypertension does not necessarily belong to the picture of arteriosclerosis. With his assistants, Hasenfeld and Hirsch, he emphasized the frequent association of high grade sclerosis of the splanchnic arteries and of the thoracic aorta, and the slight, often clinically not demonstrable hypertrophy of the left ventricle. He formulated, as did Huchard, the determining influence of renal function for the development of hypertension, thus paralleling the views of Bright and Fahr and foreshadowing the modern work of Goldblatt and others.

In Senator's classic "Disease of the Kidney" (1902), little mention of blood pressure is found other than a brief note regarding "increased pressure in the aortic system." In contrast, Litchwitz (1921) in "The Practice of Kidney Diseases" gives a most complete modern presentation of essential hypertension, "primary arteriosclerotic nephrosclerosis," a synonym

to Fahr's "red granular kidney," and the "genuine contracted kidney of the pathologists." Litchwitz and Fahr both portray a splendid etiologic and clinical picture of essential hypertension as we know it for the most part today. Fahr discusses under etiology such factors as age, heredity, overnutrition, alcohol, tobacco, gout, diabetes, and under symptomatology the heart, kidney, uremia, the blood, the retina, and vascular symptoms. Litchwitz emphasizes the importance of the patient's psyche, and of various affective disturbances, vasomotor irritability, the relation to migraine and epilepsy, social equivalents of frustrations, sorrow, urgency of the times, the relationship to angiospastic situations, treatment, etc.

#### EXPERIMENTAL HYPERTENSION

While various investigators had previously attempted to produce experimental hypertension in various ways, it remained for Harry Goldblatt to offer clear evidence of the production of persistent hypertension by placing specially devised silver clamps about the main arteries of one or both kidneys, thus producing varying degrees of renal ischemia. Starting work in 1928, he first published his results in 1932. A complete summary of his investigations may be found in the Harvey Lectures for May 19, 1938, entitled "Experimental Hypertension Induced by Renal Ischemia."

Much water has gone over the dam since these beginning experiments of Goldblatt. Experimental and clinical investigators from this country and abroad have attempted to validate or amplify Goldblatt's hypothesis. Among these workers may be mentioned Page, Keith, Schroeder, Steele, Katz, Leiter, Oppenheimer, Harrison, Weiss, Prinzmetal, Alving, Christian and many others. For the most part Goldblatt's conclusions have been amply confirmed. There is considerable difference of opinion, however, as to their clinical application.

Hoping to establish further a causal clinical relationship between the kidney and hypertension, as well as to direct intelligent therapeutic aid to the patient, Schroeder and Fish advised nephrectomy in seven patients exhibiting arterial hypertension with organic renal disease. Their results were as follows:

Two were markedly improved, and two slightly improved, but all remain actually or potentially hypertensive. This form of therapy may prove of benefit, but, it seems, only in patients in whom the existence of hypertension is of short duration and in whom arteriolar sclerosis of the other kidney is not advanced. Its use is limited, therefore, to a small number of individuals.

## CLASSIFICATION

It is becoming increasingly clear, particularly in the past decade, that arterial hypertension *per se* is not a disease sui generis, but rather a symptom or symptom-complex which occurs in a large variety of disorders. In this sense hypertension may be considered as secondary; that is to say, hypertension secondary to or accompanying some well understood primary disease process. Likewise the group known up to now as essential hypertension, implying a primary or idiopathic hypertension ("self-existing; having no obvious external exciting cause"), has become increasingly smaller as the underlying disease processes responsible for them have become known. In fact, one may predict with fair assurance that within the next decade or so most, if not all, the cases of so-called "essential" hypertension will be shown to be secondary in nature and the causative disease proven. Even now each case of clinical hypertension should be scrutinized with all possible care and with all modern diagnostic procedures to the end that the probable cause of the hypertension be discovered. For this purpose it is desirable that the now known causes of hypertension be understood and that a working classification of hypertension be made available.

Keith in 1927 divided his cases of hypertension into three groups: *benign*, *severe benign* and *malignant*. Four years later, based largely on histologic study of the arterioles from biopsy material, he classified his cases into five groups: chronic glomerulonephritis (*Group I*), and diffuse arterial disease (*Groups II, III, IV and V*), depending on the degree and severity of the vascular process. In 1939 he still further defined his classification as diffuse arteriolar disease with hypertension, *Groups I, II, III and IV*.

With increasing study and knowledge of arterial hypertension, other organs or groups of organs other than blood vessels and kidneys are known to be associated with this finding, and all may be grouped under the four systems: genitourinary, nervous, endocrine and vascular. Schroeder and Steele have offered the most comprehensive classification that I have seen and, with their permission, I have the privilege of reproducing their "Table of Classification of Hypertension" (Tabulation).

This classification of Schroeder and Steele merits careful and prolonged study, together with an understanding of the experimental and clinical work which has led up to its organization. With a thorough understanding of these many vari-

# TABULATION

ANALYSIS OF ARTERIAL HYPERTENSION (ELEVATION OF DIASTOLIC PRESSURE) ACCORDING TO FOUR SYSTEMS AFFECTED BY THE ASSOCIATED DISTURBANCES\*

I Renal parenchyma.		II Nervous system.	III Endocrine system.	IV Arterial vascular system.
A. <i>Experimental Lesions Resulting in Hypertension in Animals</i>				
Röntgen sclerosis of kidneys Chemical nephritides (oxalate) Serum nephritis Reduction of renal substance Constriction of renal vein Ureteral ligation	Removal of carotid sinus and aortic depressor nerves Intracisternal injection of kaolin Hypothalamic injury Increased intracranial pressure	Injections of estrogen and pitres- sin (beta hypophamine) result- ing in renal lesions like those found in eclampsia (blood pres- sure not stated)	Partial constriction of renal artery High intake of vitamin D and cholesterol	
B. <i>Lesions Associated with Hypertension in Man (partly after Fishberg)</i>				
Renal disease with renal failure: Glomerulonephritis (especially chronic) Urinary obstruction Polycystic kidneys Necrotizing nephroses Suppurative nephritis (rare) Pyelonephritis	Tumors of brain, etc., giving rise to increased intracranial pres- sure. Diseases of the brain stem (bul- bar poliomyelitis, etc.)	Pituitary basophilism Tumors of adrenal glands Tumors of ovary (arrhenoblas- toma) Ovarian hypofunction (?)	Obstructive arteriosclerosis of renal artery Periarteritis nodosa of renal artery Coarctation of aorta Lead poisoning	
C. <i>Clinical Phenomena Associated with So-Called Essential Hypertension</i>				
Renal diseases without renal failure or antecedent hyperten- sion (Renal hypertension)	Diencephalic syndrome (Nervous hypertension (?))	Disturbances of the endocrine system (Endocrine hypertension (?))	Arteriosclerosis (Arteriosclerotic hyperten- sion (?))	

\* From "Studies on Essential Hypertension," by Henry A. Schroeder and J. Murray Steele. Arch. Int. Med., 64: 927-951 (Nov.) 1930. Reproduced by permission of Dr. Schroeder.

eties of disease which may produce hypertension, or with which hypertension is associated, and with its application to the analysis of the individual case, one should be intellectually at least well oriented in the modern approach to the diagnosis and treatment of "essential" hypertension.

### TREATMENT

As may be inferred from the foregoing, the treatment of the individual case of hypertension must be preceded by a most careful *analytic study* as to its cause. It is obvious that the treatment of hypertension *per se*, without the most careful diagnostic procedures to rule out certain very obvious pathology, may result quite unfortunately. For example, if one attempts to treat the *symptom* hypertension without a clear understanding or analysis of its cause (so far as that is possible today), one may overlook such definite and serious pathology as chronic glomerulonephritis, chronic solitary or bilateral pyelonephritis, Cushing's syndrome, suprarenal tumor, coarctation of the aorta, polycystic disease of the kidneys and many others, so that, in the remarks to follow, it is assumed that these preliminary diagnostic procedures have been carried out, and one is more or less thrown back on the necessity of advising whatever measures are available and necessary for the treatment of the hypertension itself.

Rather than attempt to cover completely the entire field of the therapy of hypertension in detail, which has been done so many times by so many more competent men than myself, I should like to refer you to Fishberg's book on Hypertension, particularly the chapter on treatment, wherein, in the greatest detail, are found most of the suggestions which I shall mention briefly in this clinic.

The treatment of hypertension is one of the many unsatisfactory chapters in therapeutics, mainly perhaps because the fundamental causes of hypertension are still so obscure. The methods advised may or may not lower the blood pressure and may or may not benefit the patient. It is evident, of course, that attempts simply to lower the blood pressure are merely treating hypertension as a symptom and not its causative disease.

**Fear of Hypertension.**—From a clinical standpoint perhaps one of the most valuable contributions the physician can make, at least to many patients with high blood pressure, is to relieve their fear of hypertension. Because of a life

insurance examination or some other type of health examination, or quite accidentally, the patient has been told his blood pressure is slightly or greatly elevated, with the result that he is immediately confused, excited and anxious, thus making his blood pressure go still higher.

One of the really successful results the physician can accomplish in such a situation is to explain to the patient carefully and soundly what hypertension is and is not, how benign it may be for many many years, how unimportant the actual level of the blood pressure is, and for the most how safely this slight increase in pressure can be ignored, only holding to certain simple and common sense rules of living and working. Many persons with simple benign essential hypertension not only need no medical care or treatment (other than perhaps this reassurance), but are better off without treatment. Persons having no symptoms except the objective finding of increased blood pressure should not be treated, assuming that the cause of the increased pressure cannot be found. In the event that anxiety and fear have caused great distress, various attempts with *mental hygiene*, *psychotherapy*, *suggestion*, etc., should be made, even at times the calling in of a psychiatrist or psychoanalyst in the event a true anxiety neurosis has developed.\*

**Occupation.**—Apart from extremely strenuous occupations involving severe physical activity, there is probably no need to change radically the patient's occupation. If it is discovered that the patient's work involves long hours of mental or emotional strain, perhaps the type of strain seen frequently in business and professional men, there should be some diminution if possible in the degree of these burdens. Frequent and increasingly prolonged *vacations*, if they can be taken with pleasure and contentment, are often helpful, but in the consideration of such holidays the question of *climate*, *altitude*, *heat* and *cold* are all to be considered. For the most part *rest* rather than strenuous activity is desirable. It is common knowledge, of course, how well many hypertensive patients do in the southern subtropical climates (Florida, for example). *Exercise* should be moderate and should always be well within the patient's ability to carry on without undue fatigue.

\* Dr. Franz Alexander in recent years has been especially interested in the role of the personality and the emotions and in various conscious and unconscious drives in hypertension—hostility, frustration, various conflicts—and has secured good results from psychoanalysis.



**Diet.**—In reference to diet, there should be perhaps some slight protein restriction to only once daily, moderate restriction in the use of salt (except in definite cardiac failure), and no severe restriction in fluid intake (except in heart failure). It has been said that the ingestion of very large quantities of fluids can elevate the blood pressure, but this I have never seen.

Perhaps more important than the type of food is the quantity. Particularly in obese individuals some definite food restriction, advice to eat sparingly without gaining further weight and restricting food to the necessary calories, is desirable. If there are no other reasons for restriction I have found no objection to the use of *alcohol* in moderate quantities. The same I feel is true of *tobacco*. Its use should perhaps be sparing and, of course, stopped entirely in the presence of tobacco angina or Buerger's disease. Some general advice as to moderation in the use of *coffee* and *tea* is indicated and, of course, they should be interdicted entirely if there is clear evidence that one or the other causes definite symptoms, such as the isolated case of coffee angina.

The markedly *obese* should certainly reduce. It is well recognized by all of us that not infrequently the loss of 10 or 20 pounds is accompanied by a varying drop in blood pressure. The necessity for reduction in the obese is particularly urgent in cardiacs and should be accomplished by reduction in calories (rather than by strenuous exercise, baths, and drugs). The administration of thyroid substance may be considered and if the patient's basal metabolic rate is low and the heart not rapid, may be cautiously administered.

In summary, then, moderation in all things, mental and physical rest, freedom from emotional excitement, pressure, strain, undue fatigue, and hurry are the major objectives in the treatment of hypertension.

**Drugs.**—Many drugs over many years have been suggested for the treatment of hypertension, but with the exception of the *mild sedatives*, such as bromides, barbiturates, chloral, etc., I personally have never seen any striking results from them. The diuretics, calcium, sulfocyanates, etc., are not valuable and the latter I believe at times may be harmful. The older clinicians used the iodides, and at times it has seemed to me that the occasional patient has been benefited. Other drugs, such as benzyl benzoate, watermelon seed, radium chloride, injections of 1 per cent sulfur in oil, and parenteral protein injection (Fishberg), are all valueless.

In recent years, particularly for the hypertension which often develops in obese women about the time of the menopause, *organotherapy* in the form of various estrogenic substances has met with some success. I personally have seen no beneficial results from their use. The same I feel holds true of liver therapy, pancreatic preparations, physiotherapy, venesection, etc., all of which have been advised and used by many men.

Many of these points will be emphasized and defined more clearly in the treatment of the individual patient which I now plan to discuss. These suggestions are simply offered as a general guide which may be followed as indicated.

Treatment of the specific *complications* of hypertension perhaps is more important than these general measures. This, of course, refers to the complications of the heart, the central nervous system and the vascular system. These likewise will be discussed in the individual case.

#### PRESENTATION OF CASES

*Case I. "Essential" Hypertension Associated with Obstruction of the Right Ureter and Right Kidney Pelvis.*—Mr. A. S., a railroad claim adjustor, fifty years of age, first consulted me in October, 1935, for "high blood pressure of three months' standing." This had been an accidental finding about three months before, at which time there was reported a systolic pressure of 245 mm. Hg. There were no subjective complaints of any nature, but notwithstanding, the patient was put to bed for the next two months. He was given digitalis tablets which he took continually up to the time I saw him. In addition, he was given a watermelon seed preparation. In spite of two months' bed rest and drug therapy, his blood pressure remained unchanged at 240. There were no headaches, dizziness, blurring of vision, dyspnea, cough, or pain of any kind. All his teeth had been extracted for relief of the high blood pressure. His appetite was good and he slept well. Ten years ago a life insurance examination showed his blood pressure to be normal. He uses no liquor, drinks coffee twice daily, and uses tobacco moderately. Of three brothers, two have high blood pressure, the older and younger.

Examination revealed a systolic pressure of 260 and a diastolic of 130, pulse 110. His heart was slightly enlarged to the left, the left border being a finger-breadth outside of the left nipple. The heart was rapid and regular but with a presystolic gallop.

This patient has remained under observation ever since and has been seen occasionally for reassurance and a general physical check up. His last visit was in June, 1940, at which time my associate, Dr. Morris Lev, found his blood pressure to be 250/140, his pulse 112. Because of his anxiety and insistence that something be done for his hypertension, which except for his own knowledge had caused him no inconvenience, various simple measures were tried, all to no avail. On various occasions he was placed on sodium sulfocyanate, the bromides and iodides, aminophyllin, phenobarbital, etc., his systolic pressure remaining from 210 to 270 and the diastolic from 110 to 160. In November, 1939, with no complaints and with a blood pressure of 260/160, I

thought I caught a pulsus alternans. The electrocardiogram showed nothing but a left ventricular preponderance with some slight slurring of the QRS complex.

From 1935 to 1938 we considered that this patient suffered from "essential" hypertension. On September 17, 1938, because of a sudden attack of abdominal and right lower back pain and hematuria, he was hospitalized and x-rays of the urinary tract with intravenous and retrograde pyelograms made. Dr. Alfred E. Jones, who saw him in consultation, believed he showed definite obstructive changes in the right ureter and right renal pelvis with obstruction of the lower third of the right ureter, caused either by stricture or a radio-lucent stone. The obstruction in the right ureter was overcome with a No. 6 F. catheter and the ureter dilated. From that time on no further symptoms from the urinary tract have developed.

However, in view of the recent work outlined above it is possible that this obstruction of the right ureter and right renal pelvis is responsible either partly or wholly for his hypertension, and since that time up to the present we have considered the indications and the possibility of surgical interference. But because our present knowledge is not definite enough in my opinion to conclude that the trouble in the right urinary tract is causative for this hypertension, I have not had the courage to advise surgical interference. It may be, if he has a recurrence of these symptoms or if he develops other symptoms, or further knowledge indicates that the kidney pathology is a contributory cause to his hypertension, nephrectomy may be advised.

*Summary.*—One sees the futility in this case of teeth extraction, watermelon seed preparations, digitalis, sulfocyanates, and other drugs for the relief of hypertension. As a matter of fact, except for this patient's moderate obesity and the episode of right-sided pain, he has no complaints. It seems to me the only causal indication for therapy is surgical interference which, as I say, I have not had the courage to advise.

(*Note.*—Dr. Lev informs me that this patient died suddenly on December 2, 1940, apparently from an extensive cerebral hemorrhage.)

*Case II. The "Hypertensive Heart" in an Elderly Man with Coronary and Myocardial Disease, Left Heart Failure and Domestic Discord.*—This patient, Mr. B. S., a merchant seventy years of age, was first seen in June, 1938, com-

plaining of dyspnea on effort, paroxysmal nocturnal dyspnea of one month's duration, and knowledge of high blood pressure for three years. Examination revealed a large plethoric, obviously ill patient, orthopneic, with moderate edema of the ankles and in considerable distress. His blood pressure was 210/100. His pulse was slow and regular, often as low as 48. His NPN, was 39 mg.

Under simple complete bed rest, digitalis, ammonium bromide and occasional tablets of nitroglycerine to relieve his dyspnea, he made prompt and satisfactory improvement. He was seen at my office for a check-up ten days after leaving the hospital and was free from distress, taking 3 grains of digitalis daily. Examination revealed moderate moisture at both lung bases. Three months later, because of a recurrence of the paroxysmal nocturnal dyspnea, he re-entered the hospital and examination again revealed additional moisture at both lung bases, enlargement of the heart to the left, heart tones slow and markedly diminished, the liver a hand's breadth below the right costal arch and moderately tender. During this hospital stay his blood pressure reached 205/140. Because of an apparent disagreement with digitalis, he was placed on tablets of urginin twice daily, and because of the persistent paroxysmal dyspnea he was given  $3\frac{3}{4}$  grains of aminophyllin each night and p.r.n. as indicated. He again made quite satisfactory progress, leaving the hospital three weeks after entrance.

The story from here continues about the same: recurring attacks of dyspnea and distress at home, followed by recurring entrances to the hospital with improvement, until finally a nurse was placed in charge at home and things went distinctly better. After some weeks of study it became clear that much of his poor progress at home, in contrast to the satisfactory progress in the hospital, was occasioned by domestic discord, and when this was taken in hand, his improvement was more sustained.

Several electrocardiographic examinations showed first and second degree auriculoventricular block, with notching of QRS, inversion of T, etc., and what Dr. Louis Katz calls "progressive coronary insufficiency."

Mr. S. continues up to this time more or less the same and, as long as he leads a quiet life, free from emotional disturbance, he does very well. From time to time it has seemed that any and all digitalis preparations disturbed him, and for the last year or two he has gotten along very well on aminophyllin and intravenous mercupurin.

The lesson I think this patient teaches is that, as a result of a rather moderate hypertension, coronary, myocardial and conduction system involvement, he has developed symptoms and signs of left heart failure. With careful management, rest and quiet, mental and emotional control, digitalis, aminophyllin and mercupurin, he has done exceedingly well considering his age, the enlargement of his heart and the more or less continuous domestic upsets which even now have not lent themselves to complete control. It is an old observation of Eden's, I believe, that in some of these elderly patients with markedly diminished myocardial reserve, the time comes when they do not react well or at all to digitalis, there apparently being so little remaining heart muscle reserve that digitalis not only is not helpful but may be harmful. This patient is

perhaps a good example of this dictum and, as stated, he has done better the past year on medication other than digitalis. This point of Eden's was called to my attention by Dr. William Brams who at the present time is taking care of Mr. S.

We have thus far considered briefly hypertension in association with urinary tract defects and the so-called hypertensive heart as a complication of essential hypertension. At this time I wish to present a patient demonstrating an entirely different type of complication, namely, what may be considered either as a patient entering the malignant phase of essential hypertension or a complication known as "hypertensive encephalopathy":

*Case III. The Malignant Phase of Essential Hypertension, Hypertensive Encephalopathy, Possible Thiocyanate Poisoning.*—Mr. H. S., a retired industrialist of seventy years, was seen in an emergency with Dr. Elbert McLaury of Hollywood, Florida, and Dr. E. Sterling Nichol of Miami. It was known that Mr. S. had had an increase in blood pressure for many years (around 200/110). He went south, as was his custom, in the early winter of 1939, and seemed his usual robust self except for recurring increasing headaches. The story which I secured upon my seeing him in March, 1939, was that, several months before, his headaches had become much more severe and later were associated with severe attacks of vertigo. When I saw him he was exhibiting an intensely active, noisy delirium, great agitation, rigidity of the neck, and a suggestive Kernig. His attending physicians had kept him in bed for several weeks and had previously placed him, among other things, on 5 grains of chloral hydrate every four hours, and when his blood pressure continued to rise, on 1.5 grains of sodium sulfocyanate three times a day.

Because of the history and physical findings, I considered, among other things, encephalitis, meningitis, brain tumor or abscess, uremia and hypertensive encephalopathy. With the continuation and progression of the delirium which at times alternated with brief periods of coma, he was transferred to the St. Francis Hospital in Miami. Lumbar puncture was performed, which showed a clear spinal fluid without increase in pressure, some increase in globulin and 28 leukocytes per cu. mm. Within twelve hours of his entrance to the hospital his periods of coma deepened and he died without the opportunity for further diagnostic or therapeutic procedures. The autopsy, performed by Dr. Frederick H. Dieterich, revealed widespread arteriosclerosis, marked kidney damage, particularly of the glomeruli, moderately enlarged heart, and some edema of the brain. Later, microscopic and bacteriologic studies of the brain revealed no evidence of inflammation or infection and the conclusion was that his death occurred as a result of hypertension, cerebral arteriosclerosis and edema, and probably hypertensive encephalopathy.

One extremely interesting question arose in this case, namely, the role of the sulfocyanates. The patient received a total of approximately 30 grains of sodium sulfocyanate in seven days without control of the blood concentration. Coincidentally with his death, a series of reports appeared in the *Journal of the American Medical Association* on the toxic

manifestations of the thiocyanates by Wall, Lindberg and Parker, and by Curtis F. Gardner of Cleveland. Interestingly enough, several of the cases reported were practically identical with the clinical and pathologic findings in this case. For example, a patient of Goldrin and Chase's, reported by Wall, Lindberg and Parker, received 9.77 gm. of thiocyanate in fifteen days and died with a clinical picture of "nausea, delirium, hallucinations, motor restlessness, nystagmus, convulsions, disorientation and coma." Necropsy revealed, among other things, cerebral edema. Gardner's patient was noisy, excited, restless. She had delusions of persecution and various sorts of hallucinations. She had received 9 gm. of the drug (135 grains) in fifteen days. In this patient the blood cyanate level was followed. Autopsy revealed generalized arteriosclerosis but no untoward findings in the brain.

The clinical picture and autopsy findings of both of these authors' patients were strikingly similar to my own, and it is suggestive that the cyanate therapy was the cause of, or at least was contributory to, Mr. S.'s death. It raises again the question of the toxic properties of sulfocyanates and of the wisdom of their use in hypertension. While it had been my practice occasionally to administer modest amounts of the cyanates in hypertension, resulting occasionally in an apparently moderate drop in pressure, since my experience with this case and from the reports in the literature I feel that the *cyanates have no place in the treatment of hypertension*, with or without blood level controls. I feel the margin between therapeutic safety and toxicity is too narrow and, in addition, that there are probably individuals who are sensitive to the cyanates and in whom the sensitivity cannot be foreseen. Further, in such patients, although the drug be stopped, some apparently progress to serious illness and/or death. For these several reasons I believe that thiocyanates should not be used. Other men are coming to this same view, among them Fishberg.

In connection with this case I should like to discuss very briefly the *malignant phase of essential hypertension* which I believe this case probably likewise represents. It is the general belief that patients with essential hypertension enter the malignant phase only after a prolonged period of high diastolic pressure which, it is thought, produces acute damage to the arterioles and elevation of intracranial pressure. One of the significant symptoms of prolonged diastolic pressure and elevation of intracranial pressure is the severe headache, which

is thought by some to represent edema of the brain. Ophthalmoscopic examination in such cases reveals papilledema, "the clinical sign par excellence." This malignant phase of essential hypertension may or may not be synonymous with so-called hypertensive encephalopathy. In any event, I think it may be valuable to refer to Fishberg's *treatment* for the malignant phase of hypertension. The reason I am including it is the feeling that possibly if we had had time to institute some of these measures, this patient's life might have been saved. His treatment includes the following: Venesection of 500 cc. of blood; lumbar puncture; hypertonic sugar solution, 50 per cent sucrose, given slowly intravenously; magnesium sulfate 20 cc. of a 10 per cent solution given intravenously in adults, slowly every one to two hours (may be also given rectally); if respiratory depression occurs, 5 per cent calcium chloride or calcium gluconate may be given intravenously.

I am presenting this next patient to illustrate the great necessity and importance of *accurate diagnosis before treatment is instituted*. I saw this girl only once when she was presented at the Wednesday afternoon Medical Conference of the University of Chicago Medical Clinics. The history and findings have been kindly given to me for presentation in this clinic by Drs. Alving and Leiter of the University of Chicago:

*Case IV. Coarctation of the Aorta and Right Hydronephrosis in a Young Girl with Hypertension.*—This eighteen-year-old high school student entered the Albert Merritt Billings Memorial Hospital for dysmenorrhea of two years' standing, which complaint incidentally bore no apparent relationship to other interesting details discovered later. Everyone who saw her was astounded by the fact that she showed a blood pressure of 170/130 on entrance to the outpatient department on January 16, 1940. The second aortic tone was increased. Examination of the heart revealed moderate enlargement, with the apex beat in the sixth interspace. The diagnosis at the time of entrance was "essential" hypertension, intact hymen and dysmenorrhea. One finds this note on the record: "This patient is exceedingly intelligent to converse with. She ranked seventh in a graduating class of 400 in a Chicago high school and received numerous scholastic honors . . . is attempting to finance her entire education herself, and the nervous background seems to be very important as a possible and probable factor in her hypertension."

The patient was operated upon on April 13, 1940, a hymenectomy being performed under cyclopropane anesthesia. Her postoperative blood pressure was 194/130. At about this time Dr. Alice Childs of the Clinic was unable to palpate the peripheral pulse in the legs and feet and was unable to obtain the blood pressure in the lower extremities; she suggested the likelihood that the patient was suffering from coarctation of the aorta. Following the patient's convalescence from the operation she was x-rayed. The report from Dr. Hodges states, "There is scalloping of the under margins of the fourth to the ninth or tenth ribs, inclusive, on each side. Impression: Coarctation of the aorta has resulted in characteristic rib lesions." Intravenous pyclography was

performed, showing "the right kidney pelvis dilated, as well as all of the calices. There is sharp angulation at the ureteropelvic junction with a definite indentation of the ureter at this point. Impression: Right hydronephrosis resulting from aberrant vessels." Glancing through her history one finds the following: "The patient has classical signs and symptoms of coarctation of the aorta, with large collateral arteries on the posterior chest wall in interscapular area. There is no pulsation of the femoral or distal arteries. There is pulsation of the abdominal aorta but diminished. (I could feel the beat after extrasystole also.) There is no sclerosis of the peripheral arteries in the upper extremity. The intercostal artery is visible below and medial to the angle of the right scapula. Several other intercostal arteries palpated over the back; one is left axilla. Impression: Coarctation of the aorta; hypertension secondary to the coarctation."

Here, then, is a striking example of the diagnosis by Dr. Childs of the congenital condition known as coarctation of the aorta, responsible unquestionably for this early severe hypertension. The lesson to be learned from this patient is obvious, that the general surgical and psychotherapeutic management would be entirely *futile* without a clear recognition of the causative pathology, namely, a congenital lesion of the aorta. (I may say, however, that the question of the hydronephrosis of the right kidney may conceivably play some role.)

For the coarctation and the consequent hypertension little, of course, can be done other than the management of this patient's general hygiene and mode of life so as not to accentuate still further the hypertension. For example, one finds a note in the chart for May 17, 1940: "Advise limited activity and  $\frac{1}{2}$  grain of phenobarbital twice daily."

*Case V. Coronary Occlusion Occurring Fifteen Months Following Splanchnicectomy for Hypertension.*—Mrs. J. P., the wife of a physician, was first seen in November, 1937. She had undergone splanchnic nerve resection for hypertension the year before, at which time the systolic pressure fell from 230 to 160. Approximately fifteen months after the sympathectomy she suffered two critical and classical attacks of coronary thrombosis, and since has suffered from precordial pain, cough, vertigo, fatigue, etc. Her blood pressure on the first examination was 140/110, but since then it has gradually and slowly risen; in March, 1938 it was 166/114, in July, 1939 190/130, and in December, 1939 180/130, and so on.

Although this patient secured a considerable drop in pressure immediately following operation, this improvement has not continued. However, the striking interest in this case is the postoperative occurrence of *coronary thrombosis*. Of course, coronary occlusion occurs all too often in patients within this age group without preceding sympathectomy or operation of any sort, and furthermore the period of fifteen months following splanchnicectomy perhaps entirely rules out a pos-



sible causal relationship. One cannot, however, help but consider the possibility that as a result of the drop in pressure following sympathectomy, the circulation in the coronary system likewise dropped or became slower, with possibly some degree of coronary insufficiency contributing to the occlusion.

One cannot, however, say with any degree of accuracy that had this patient not had sympathectomy she would nevertheless have suffered this cardiac complication. This is the only case in my own experience. Furthermore, I have been unable to find a similar one in the literature. Nevertheless, the only temporary improvement in blood pressure plus the occurrence of this coronary episode add support to the view that, at least up to the present, sympathectomy of any type has not progressed far enough to justify its recommendation generally to hypertensive patients.

#### THE EMOTIONAL FACTOR IN HYPERTENSION

In conclusion I should like to refer briefly to one practical point in treatment and mention the recent work of Alexander, Saul, Miller, Weiss and others on the role of the emotions in the genesis of hypertension and what may be done in a practical way toward amelioration. In a recent symposium on hypertension (Psychosomatic Medicine, Jan. 1939) Saul wrote on "Hostility in Cases of Essential Hypertension" and Miller on "Blood Pressure and Inhibited Aggressions." From a practical therapeutic standpoint, however, Edward Weiss, I believe, states the situation in the simplest terms and I can do no better than quote his concluding paragraph completely:

"To advise the individual involved in mental conflict not to worry is absurd, especially when, as is so often the case, no concerted effort is made to find out what is disturbing him. Too often the physician is satisfied that there are no problems disturbing the patient after he has inquired, 'Are you worried about anything?' and has received a negative reply. Most of the time the patient really does not know just how much he is disturbed, nor does he relate the factors actually responsible for his discontent. He is much more apt to project his worries into questions about his blood pressure, heart, brain, and kidneys. Careful inquiry will bring out that his fears are exaggerated and that the reasons he assigns for them are illogical. *There is only one approach that has any merit; that is, to encourage the patient to talk about himself as a person rather than as a medical case.\** This will permit some insight

\* *Italics mine.*—W.W.H.

into conflict situations and lead often to some relief of anxiety, which is closely related to the high blood pressure. Although this approach does not offer a complete solution of the hypertensive problem and does not even apply to all patients, it is a practical method of dealing with a set of important factors that may be modified, whereas the constitution of the individual cannot be touched. It is an approach heretofore not sufficiently practiced. We are too much concerned with physical measurements in hypertension—the blood pressure figures, the percentage of renal function, the size of the heart, the electrocardiographic tracing, the amount of retinal sclerosis—all of which are essential in the study of the hypertensive person but give incomplete information from the standpoint of the total evaluation of the patient. They should represent the beginning and not the end of study. We are too little concerned with the emotional life, which may hold the key to the satisfactory management of the hypertensive patient.”



## CLINIC OF DR. JESSE R. GERSTLEY

### MICHAEL REESE HOSPITAL

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#### ANOREXIA OF PERPLEXING ORIGIN

THIS case should be of interest to students of general pediatrics, endocrinology, neurology and psychiatry. The patient, a boy eleven years old, entered Sarah Morris Hospital December 6. The history obtained by the intern from the mother is as follows:

He was perfectly well, bright, and a leader in his class until he went to camp last summer. Following his return in August, he showed a tendency toward drowsiness in the afternoons. This was barely noticeable at first, but in a short while it seemed to cause an entire change in his activities. First he took short naps after lunch. Then the naps became longer. At times he would get up and go out to play with the boys, but soon he would come in again, tired and sleepy. The drowsiness increased so that he slept most of the afternoon.

The mother reports that he voided 2 to 3 quarts of urine daily and that his voice had become low and husky. He had lost his normal appetite and now ate almost nothing. Occasionally he complained of pain in the right side of the abdomen. There were no signs of infection, such as fever, cough, or sore throat. The mother was not really alarmed until two weeks previously when he started vomiting. Now the boy retains practically nothing and has lost 9 pounds in the last two weeks; he still, however, maintains his high scholarship. He weighed 84 pounds at camp. Other than this, there is nothing more in his or in the family history.

#### EXAMINATION

*Question:* "How are you feeling?"

*Answer:* "O.K." (said in a low husky voice).

*Question:* "Are you hungry?"

*Answer:* "No."

For an eleven-year-old boy, as you can see, he is quite tall; he is 61 inches in height and weighs 77 pounds (average for this age 55 inches and 73 pounds). His weight for his height should be 95 pounds. You see his nutrition is not good; he shows the loss of weight, and his skin is unusually dark. Notice the staring expression and a slight lid lag. The slight right internal strabismus is of long standing, according

to the mother. His genitals are large for a boy of his age and there is considerable growth of pubic, but no axillary or facial, hair.

*Summarizing*, we have then a rather sudden onset of the condition following a period in camp four months ago. Then came drowsiness, anorexia and, in the last two weeks, vomiting which has become severe. The physical examination shows a large boy, in poor nutritional state, with some precocious sexual development. His eyes just suggest hyperthyroidism, but there are no other signs or symptoms. He is profoundly disinterested in his environment and his peculiar mentality is revealed by his laconic answers. During the entire month he has been here his conversation seemed limited to the following. When asked "How are you?" he replies in an apathetic adult voice "O.K." or "I'm all right." In answer to "What do you want to eat?" he replies "I'm not hungry." He never speaks spontaneously and shows little interest in his surroundings, but his past record in school and even his present appearance suggest a high intelligence.

#### DIAGNOSIS

This boy presents one of the most perplexing diagnostic problems of my entire experience:

*Acute Encephalitis?*—Of course, the first condition suspected is acute encephalitis. He was well until going to camp this summer, following which he has become drowsy and lethargic. However, there is no history of any febrile disturbance. There is no rigidity of the neck or of the back as in poliomyelitis, no Brudzinski and no Kernig sign. The drowsiness has progressed steadily for four months and was only very slight following his return from camp. Furthermore, it was originally limited to afternoons, while he was bright and alert in school in the mornings. And finally the lumbar puncture immediately after admission showed fluid of normal character: no increased pressure; cells not increased; sugar 34 mg., chlorides 673 mg., and total protein 74 mg. per cent; no excess of globulin; Wassermann negative; and colloidal gold curve flat.

*Pituitary Involvement?*—With a history of frequent urination, precocious sexual development and something suggestive about the eyes, one might suspect the pituitary. Eye examination by our specialists showed normal fundi, normal visual fields and pupillary reflexes. The x-ray of the sella turcica seemed normal.

*Diabetes Insipidus?*—As regards diabetes insipidus, the water balance showed an intake of 1500 cc., with an output of about 1200 cc.

*Results of Routine Diagnostic Procedures.*—Simultaneously we instituted the routine diagnostic procedures: Repeated urinalyses, erythrocyte counts, leukocyte counts, differential leukocyte counts and hemoglobin estimations showed no deviations from the normal. The blood pressure was constantly low, averaging about 90/50. The blood Wassermann reaction was negative, as were also the various tests for tuberculosis. Blood calcium, phosphorus, nonprotein nitrogen and total protein were similarly within normal limits. But *blood uric acid* was 9.4 mg. per cent and a repeat showed 8.9 mg. per cent.

*Chronic Intestinal Obstruction?*—In view of the history of abdominal pain associated with anorexia and persistent vomiting, chronic intestinal obstruction due to some malignancy is a possibility, but he continued to pass feces and flatus. The barium meal gave no clue, and the subsequent course proved otherwise.

*Other Conditions Considered.*—His peculiar apathetic state and staring expression continually suggested something *cerebral*. Examination by neurologic consultants revealed nothing. In view of the abdominal pain, could it perhaps be a *kidney* or *adrenal tumor* with cerebral metastases? Routine x-rays of the chest and abdomen gave no help. Functional tests of the kidneys showed no abnormality.

Was his deep voice part of the picture, or was it due to some *local abnormality*? Laryngologic examination was negative.

*Results of Endocrine Study.*—The finding of a *high blood uric acid* led to our suspecting some type of endocrine disturbance and, while all the above examinations and consultations were being held, we made a specific endocrine study which I shall summarize:

Could the *pancreas* or *liver* be involved? A number of estimations of the fasting blood sugar yielded hypoglycemic values, as low as 42 mg. per cent. We tried his dextrose tolerance with intravenous injections of  $\frac{1}{2}$  gm. of dextrose per kg. of body weight. One-half hour after sugar administration the blood sugar level rose to 213 mg., dropping to only 115 mg. per cent at the end of two hours. This is a decidedly diabetic type of curve. In discussing the matter with Dr. Soskin of our department of metabolic research, the test was interpreted

as indicating some liver dysfunction. Simultaneously a 50 per cent retention of bromsulfalein corroborated this finding. However, the blood cholesterol and cholesterol esters were found to be normal in frequent tests, and to our utter mystification at a later date the dextrose tolerance curve and the bromsulfalein excretion returned to normal. We therefore decided that the findings suggesting an abnormal liver metabolism might have been due to inanition, which we had in the meantime corrected, or might be secondary to thyroid, adrenal cortex, or anterior pituitary dysfunction.

How about the *thyroid*? Here again the results were contradictory and inconclusive. There was mild exophthalmos, but the pulse rate ranged around 70 per minute and there were no clinical signs or symptoms of hyperthyroidism. The basal metabolic rate determinations gave values of minus 22 per cent and minus 34 per cent. But radiologic examination of the centers of ossification showed that the patient's bone age was consistent with his chronologic age. Remember also that the cholesterol and cholesterol esters were normal.

The presence of weakness, vomiting, pigmentation, low basal metabolic rate and low fasting blood sugar with evidence of liver deficiency suggested *Addison's disease*, but the negative tuberculin reaction ruled out the commonest etiologic factor. Furthermore, the blood sodium was 561 mg., potassium 136 mg., and the nonprotein nitrogen not increased, *i.e.*, 33 mg. per cent. Urinary chloride excretion was normal. The patient's poor clinical condition precluded a test with a high potassium diet.

By exclusion we return again to the *pituitary*. The extreme anorexia, weakness, hypotension, low fasting blood sugar and evidence of liver deficiency were consistent with pituitary cachexia. In spite of the previous negative findings we tried a therapeutic test with an anterior pituitary preparation (*Thyone*) which Dr. Soskin had found to be effective in a proved case of pituitary cachexia. There was no benefit.

*So we were back again where we started.* The metabolic and endocrine studies as a whole were interpreted as indicating the presence of some endocrine dysfunction, but did not permit the diagnosis of a primary dysfunction in any particular group.

#### COURSE

For about a month we have been carrying on these tests. During this time there has been no change in the boy's physical condition; only an intensification of his anorexia and

lethargy. His pulse averages 60 to '80. He never complains of hunger and consistently refuses to eat anything other than an occasional swallow of water or milk. The slightest amount of anything solid, such as cereal, bread or meat, results in immediate vomiting. We sustained him for a week on intravenous fluids, salt and glucose. Then we introduced feedings by nasal catheter. Because of fear of liver damage we were very cautious at first, but we subsequently found that he retained a very considerable diet. During the last few weeks we have kept the tube in his stomach constantly, removing it only for cleansing, and he has retained a really high caloric diet. In spite of this, however, he is gaining little weight and his mental condition remains unchanged—an attitude of utter indifference. To our chagrin the moment the tube is removed, any effort at feeding by mouth results in vomiting, but immediately the tube is reinserted, he retains and digests large quantities, although he dislikes the tube. Apparently the improvement in the liver function tests was associated with improvement in his nutrition.

The absence of any decided changes in the physical condition, the peculiar mentality, and the failure to respond to the pituitary preparation led to the suspicion of a condition which I am very hesitant about diagnosing in a boy of this age—*anorexia nervosa*. In desperation we called in the psychiatrist. The psychiatrist examined the child first on January 12, and after several examinations did what the rest of us had done, scratched his head. He reported that the child was apathetic, speaking only in a low voice. He seemed extremely dependent upon the nurses, asking them to help him with simple tasks that he was quite able to perform. His urgent problem was his inability to eat. In spite of his appreciation of the fact that he must eat and his repeated statements that he would, he persistently refused every meal. He showed anxiety for the distress that this symptom was causing his mother and sister. But he showed good intelligence, excellent orientation in all fields, and good contact with his environment. Subsequent examination continued to show the picture of a state of depression which was no different from the findings in a purely functional state. He would lie in bed for hours, seemingly asleep, and yet aware of what was going on. He was unaware of his poor prognosis and the general findings were present in a setting of encouragement and stimulation. In short, Dr. Kassanin, the psychiatrist, first suspected schizophrenia because an athletic, sociable, happy



youngster with indefinite neurologic findings had become morose, withdrawn and lethargic. But the history revealed that the boy's personality had always been of a definitely outgoing type, affection for his relatives finding free expression. He showed all the physical manifestations of a profound depression, with no evidence that he actually felt depressed.

*So we were back once more where we started!*

It has always been my habit whenever in a real dilemma to try to check back and see if one can simplify and clarify or discard conflicting evidence. As you know from previous clinics, I lay particular emphasis upon the importance of the history. Is it possible that the intern, through lack of experience, or the mother, had failed to give us the entire story? I sent for the father, asking him to come to my office. Here in an hour's cross examination I finally learned facts of importance, of *vital* diagnostic importance. Our patient was not taken ill after leaving camp last summer. The father admitted that symptoms had been present *before* the boy had gone to camp. One year ago on an auto trip of a hundred miles it was necessary to stop many times for the boy to urinate, and previous experience with regard to his thirst led to packing the auto with several bottles of drinking water. This polyuria was of such importance that it caused him great inconvenience in camp and led to his being housed close to the toilet. Simultaneously he developed a noticeable craving for sweets. The father had noted some drowsiness of the child even before going to camp, and the camp director had mentioned that the child was lethargic. However, the mentality had been unaffected; the boy was bright and alert in school and showed no change in intelligence, even up to the time of admission to the hospital.

Here then, gentlemen, is an entirely *different* story and picture: A symptomatology slowly progressive over a year's time characterized by diabetes insipidus (which seems to have corrected itself), mental change, progressive anorexia, and now vomiting. In spite of the absence of physical findings, the gradually progressive nature of the ailment plus the loss of weight in spite of sufficient calories, is highly suggestive of malignancy. I suspect the location to be *cerebral*.

#### SUBSEQUENT COURSE

Some days after this presentation it was noted that the boy's pupils did not react well to light but, subsequently, they reacted normally. On January 24 there was some limitation

of upward gaze. A few days later the boy could no longer wrinkle his forehead or smile, or at any rate would not. In spite of the gavage, he still lost weight. By February 4, there was a slight diminution in the right abdominal and cremasteric reflex. By the end of February the drowsiness increased to semicoma, with involuntary urination and defecation. Ventriculography performed on March 7 led to the diagnosis of an inoperable cerebral neoplasm. The lumbar puncture in February had shown xanthochromic fluid under a pressure of 340 mm. of water, dropping to 190 after removal of 10 cc. of fluid; a total of 27 cells, 80 per cent lymphocytes, and a total protein of 133 mg. per cent.

The optic disk showed no change until March 12, when early atrophy, especially of the left, was noted. By March 23 definite elevation was present.

The boy fell into deep coma on March 23 and died on March 26.

**AUTOPSY.**—Without reviewing all details, the essential findings lay in the brain. At the base of that organ, behind the optic chiasm and replacing the substance of the base of the third ventricle, was a firm, ovoid mass measuring 1.5 by 2 cm. in greatest diameters, causing an indentation on the posterior portion of the optic chiasm and the anterior border of the pons. The third nerve passed over this mass. The tumor compressed the right basis pontis and occluded and pushed the Sylvian aqueduct to the left. No vestige of the pineal body was found in the pineal recess. The tumor had invaded the third ventricle, which in the posterior part was dilated and pushed posteriorly and upward. The tumor had almost completely destroyed the corpus callosum and had extended into the widely dilated lateral ventricle from the region of the tegmentum.

I will not go into the entire details now, but for those of you who are interested, this tumor proved a very rare one—a *teratoma of the pineal body*, and the entire pathologic findings will be reported in detail elsewhere.

#### DISCUSSION

This case has been of especial interest to me. It has always been my hobby to try to simplify medicine and to see what one can learn from a careful history and conscientious physical examination frequently repeated. In this instance the diagnosis was really established by simple clinical procedures. Forgetting all the laboratory findings, we were able

to rule out ordinary diabetes insipidus by measuring fluid intake and excretion. The fact that the boy retained a high caloric diet with much cream and with no digestive disturbance when it was given to him by tube ruled out gastro-intestinal or liver disease. But in spite of this he lost weight. Still clinically he was no hyperthyroid.

Those of us who have been practicing pediatrics for many years know that pupils not reacting to light cannot be overlooked. And changes in the superficial reflexes, even if mild, have much significance. True, these findings did not come until late in the course of the disease, but they did come. And finally, of course, there is the history; in the conscientious practice of pediatrics a *careful history* is, in my opinion, equal to or even greater in importance than physical examination.

In conclusion, then, let me leave you with the idea that although laboratory tests of all sorts are a very great aid and will undoubtedly do a great deal to aid our insight into the metabolism of disease, still a painstaking history and conscientious frequently repeated physical examination are still the mainstays of good clinical pediatrics.

## CLINIC OF DR. R. R. GREENE

### ST. LUKE'S HOSPITAL

#### ENDOCRINE THERAPY FOR GYNECOLOGIC DISORDERS

IN the time allotted, any attempt to discuss the whole field of gynecologic endocrine therapy would result in a presenta-

TABLE 1  
ESTROGEN PREPARATIONS

Route of administration.	Scientific name.	Commercial name.	Labeled potency.
Intramuscular	Estradiol dipropionate	Di-Ovocylin (Ciba)	mg.
	Estradiol benzoate	Ben-Ovocylin (Ciba) Progynon-B (Schering) Dimenformon benzoate (Roche-Organon)	mg. Rat units (10,000 R.U. = 1.66 mg.)
	Estrone	Theelin (Parke-Davis) Estrone (Abbott) Estrone (Lilly)	Internat. Units (10,000 I.U. = 1.0 mg.)
	Estrone-like preparations*	Estrolin (Lakeside) Amniotin (Squibb) Menformon (Roche-Organon) Folestrin (Armour)	Internat. Units
Oral	Estradiol	Ovocylin (Ciba) Progynon-DH (Schering) Dimenformon (Roche-Organon)	mg.
	Estrone-like preparations*	Amniotin (Squibb) Folestrin (Armour)	Internat. Units
	Estriol	Theelol (Parke-Davis) Estriol (Abbott) Estriol (Lilly)	mg.
	Estriol glucuronide	Emmenin (Ayerst, McKenna and Harrison)	"Day oral units"
Inunction	Estradiol	Ovocylin ointment (Ciba) Progynon ointment (Schering)	mg.
	Estrone-like preparations*	Menformon ointment (Roche-Organon)	Internat. Units

\* Contain mixtures of estrone, alpha estradiol, beta estradiol and equilin.

tion of only generalizations, and the medical literature already contains too many articles consisting of vague recommenda-

tions and all-embracing generalizations on this particular subject. I shall, therefore, attempt to be specific and consider one

TABLE 2  
ANDROGENS AND PROGESTATIONAL PREPARATIONS

Route of administration.	Scientific name.	Commercial name.	Labeled potency.
<i>Androgens</i>			
Intramuscular	Testosterone propionate	Perandren (Ciba) Oreton-B (Schering) Neo-Hombreol (Roche-Organon)	mg.
Oral	Methyl testosterone	Not yet available	mg.
Percutaneous	Testosterone or methyl testosterone or testosterone propionate	Perandren ointment (Ciba) Oreton ointment (Schering) Neo-Hombreol ointment (Roche-Organon)	mg.
<i>Pregestational Preparations</i>			
Intramuscular	Crystalline or crude progesterone	Lutocylin (Ciba) Proluton (Schering) Lipo-lutin (Parke-Davis) Progestin (Lakeside) Progestin (Roche-Organon) Progestin (Upjohn) Progestin (Lilly) Progesterone (Armour)	mg. or Internat. Unit (1 I.U. = 1.0 mg.)
Oral	Pregneninolone (ethynyl testosterone or anhydro-oxy-progesterone)	Pranone (Schering)	mg.

TABLE 3  
GONADOTROPIC HORMONES

Type.	Commercial name.	Labeled potency.
Chorionic	Anterior-Pituitary-Like Gonadotropic Hormone (Lakeside) Antuitrin-S (Parke-Davis) Follutein (Squibb) Pranteron (Schering) A.P.L. (Ayerst, McKenna and Harrison)	Internat. Units on all recent products
Equine	Gonadogen (Upjohn) Gonadin (Cutter) Anteron (Schering)	Internat. Units
Anterior pituitary extracts	Prephyrin (Chappel) Gonadotropic factor (Ayerst, McKenna and Harrison)	Rat Units

phase of the subject, namely, *methods of treatment*. This will include a discussion of the potency of the various sex hormones and the possible routes of administration with their advan-

tages and disadvantages. A few very positive and possibly heretical assertions must be included. Time will not allow detailed justification of these assertions. They are based, however, on a familiarity with and experience in experimental endocrinology and, more important, on observations made in the clinical use of these hormones on humans.

### TERMINOLOGY

There has been confusion and too much multiplicity in the names used for the various sex hormones. In order to clarify the situation, the scientific and some of the better known commercial names for the sex hormones are shown in Table 1. A few definitions of terms must also be given to aid clarity and to avoid ambiguity.

**Estrogens.**—The term "estrogen" is applied to any substance that has activities resembling those of the female sex hormone. Included in this category are the natural estrogens like *estradiol*, which is presumably the true female sex hormone as produced in the ovary, and *estrone* and *estriol*, which are both less potent excretion products found in the urine. Several other estrogens are found in mare's urine, but since they are not found in the human they need not be discussed here. More important is the discovery that many substances which are chemically more simple than the natural estrogens also have potent estrogenic properties. One of these substances is *stilbestrol*, which is being used clinically but is not yet sold in the open market.

**Androgens and Progestational Preparations.**—An "androgen" is any substance having powers resembling those of the male sex hormone. Many natural androgens are known to exist. *Testosterone* is presumably the true male hormone as produced in the testis. The combined form of testosterone (*testosterone propionate*) is the only androgen of therapeutic importance.

*Progesterone* is the corpus luteum hormone. Any substance which simulates the activities of progesterone is known as a "progestational substance." *Pregneninolone*, an orally active progestational substance, will be discussed later.

**Gonadotropic Substances.**—"Gonadotropic substances" or *gonadotropins* are not sex hormones but substances which stimulate the gonads (ovary or testis) to produce sex hormones. There are several types of gonadotropins in clinical use. Included are pituitary extracts (*pituitary gonadotropins*), extracts of human pregnancy urine or placenta (*chor-*

*ionic* gonadotropins) and extracts prepared from pregnant mare's serum (*equine* gonadotropins).

#### ROUTES OF ADMINISTRATION

The sex hormones are chemically stable substances and can be administered by several different routes. Selection of the most effective route for hormone administration depends on the particular nature of the hormone used. The sex hormones are quite insoluble in water. Therefore, to be given hypodermically in any effective amount they must be in solution in oil. The gonadotropins are complex protein hormones which are completely destroyed by the stomach acids or are digested by the digestive enzymes. *Oral* administration of these substances, therefore, is completely valueless.

**Parenteral Administration.**—At the present time the sex hormones are most efficient, or have the greatest clinical effect per milligram of hormone, when given *intramuscularly*. One author has recently claimed that *subcutaneous* administration has some advantages over intramuscular administration. Practically, I doubt that this is true. The oil solvent for the hormone is very slowly absorbed. With subcutaneous administration, a residue of the slowly absorbing oil forms a noticeable swelling under the skin which is objectionable to the patient. The oil residue after intramuscular administration, on the other hand, is not palpable.

The *gonadotropins*, as has been noted, are effective *only* by the *parenteral* route. Since they are water soluble, they may be given either subcutaneously or intramuscularly.

**Oral Administration.**—In the case of the *natural estrogens*, oral administration is relatively inefficient and much more costly to the patient than intramuscular administration. Authorities do not agree as to the exact ratio of effectiveness between these two methods of administration, but at least nine-tenths and probably more of the effectiveness of most natural estrogens is lost when they are given by mouth. This method of administration is of value only when the cost of medication does not worry the patient or when the estrogen dosage requirement is very low. The relative potencies of different estrogens, when given orally, will be discussed later.

One of the synthetic estrogens, *stilbestrol*, has a clinical advantage over the natural estrogens in that it is very effective by mouth. Its oral effectiveness is only a little less than its effectiveness by the intramuscular route. Its desirability as a therapeutic substance is also enhanced by its low cost. How-

ever, it has one definite disadvantage in that it causes undesirable *side reactions* in a certain proportion of patients. I am convinced that most side reactions from stilbestrol are due to *overdosage* and that with careful use of smaller doses, this substance will prove to be clinically valuable. Since at the present time this substance cannot be sold in this country, I shall not discuss its use in any detail.

*Progesterone* has no effect by mouth and is completely wasted when given by this route. The synthetic substance, *pregneninolone*, which has a progesterone-like effect on the uterine endometrium, is fairly effective on oral administration. This substance has been extensively advertised as an oral substitute for progesterone. I believe, however, that too little is known about it to justify its extensive use in humans. It is true that in the experimental animal *pregneninolone* causes characteristic progestational changes in the endometrium. But it also has other effects on the uterus and vagina which are characteristic of stimulation by estrogens. Its use, for example, to quiet the irritable uterus in threatened abortions (as progesterone is supposed to do) cannot be recommended until there is evidence that it will have this effect in the human. It has been found in our laboratory that *pregneninolone* has an estrogen effect on the uterine motility of the rabbit in that it stimulates contraction and increases irritability.

The one active androgen that can be purchased at the present time (*testosterone propionate*) is practically completely inactive by mouth. This statement is made in spite of the claims of one worker that testosterone propionate is active by mouth when given with bile salts. His claim is not supported by adequate evidence, and experimental findings in our laboratory indicate the contrary. Luckily, testosterone propionate is only sold in ampule form for hypodermic administration.

There is only one known androgen that is at all active by mouth. This substance, which is not yet on the market, is *methyl testosterone*. I have had patients respond to this substance by mouth in the same manner as they respond to testosterone propionate intramuscularly. The necessary dosage of methyl testosterone by mouth is relatively tremendous, however, and it is doubtful that the pharmaceutical houses will be able to sell it cheaply enough so that it will have much practical clinical value.

**Percutaneous Administration.**—The sex hormones are absorbed through the skin, enter the general circulation, and



have systemic effects. This has been demonstrated on the experimental animal in several laboratories, including our own. When applied in the form of an *ointment*, the sex hormones are not as potent as when given parenterally. Estrogens and androgens are one-sixth to one-seventh as potent by this route. We have found that progesterone has relatively even less potency when given percutaneously. Inasmuch as the skin of the laboratory animals differs from that of the human, it is not permissible to conclude that the same differences between percutaneous and parenteral administration of sex hormones apply to the human. There are several reports demonstrating that percutaneously applied estrogens and androgens are effective in the human, but there are no good quantitative data as to just how effective they are. Such data are admittedly difficult to obtain in the human.

In a series of menopausal patients, I have found that relatively tremendous amounts of estrogens (in comparison to the necessary intramuscular dose) must be given percutaneously to control symptoms. I believe that, in general, percutaneous administration of sex hormones has a practical clinical value only for patients requiring a *low dose*. A further possible indication might be as supplementary therapy to prolong the time interval between hypodermic treatments, thus decreasing the necessary frequency of office visits.

Although the estrogen which is absorbed through the skin enters the general circulation and has systemic effects, it is at its greatest concentration at and near the point of application. This fact has been used to advantage in certain special circumstances. *Estrogen ointments* have been rubbed into *under-developed breasts* in order to obtain maximal stimulation and growth of the breast with minimal systemic effects. For this same reason *estrogen suppositories* have been recommended in the treatment of *senile vaginitis* in the postmenopausal human. The estrogens increase the blood supply and stimulate growth and general resistance of the atrophic vaginal mucosa. *Estrogen suppositories* have also been recommended in the treatment of infantile *gonorrheal vaginitis*. Estrogen therapy for this condition is definitely indicated and, in my experience, is very successful if *adequate* therapy is given. However, I do not approve of the use of estrogen suppositories in children. The advantages of a good local vaginal effect with a minimal systemic effect achieved by this method are far out-weighed by the danger of genital fixations and aversions induced by this form of treatment. This condition can better be cured by

three or four parenteral administrations of *estradiol dipropionate*; 1 mg. on making the diagnosis, 1 mg. a week later, 1 mg. after three weeks and, for additional safety, another milligram at the fifth week.

**Pellet Implantation.**—The sex hormones have been administered in the form of solid pellets implanted subcutaneously through a surgical incision or by means of a trocar. A clinical effect lasting for several months is obtained from one implantation. Considering the effect per milligram of substance, this is undoubtedly the most efficient method of hormone administration.

In treating gynecologic disorders, however, it has several obvious *disadvantages*. The procedure necessitates a complicated technic and special equipment; the pellets are not commercially available; the effect obtainable from a pellet of a certain weight is not known with any degree of accuracy, and therefore dosage cannot be readily controlled. Furthermore, in gynecologic therapy, with the exception of menopausal patients, interrupted treatment or one short course of treatment is desired rather than the long continuous hormone absorption obtained by the implantation method.

#### THE POTENCY OF VARIOUS HORMONE PREPARATIONS

**Inactive Preparations.**—It may seem out of place in this discussion to mention the fact that many preparations sold to and used by the physician are totally inactive and useless. Some of the less scrupulous pharmaceutical firms, however, advertise these compounds very extensively and occasionally the physician obtains good results with them. Such occasional good results obtained with these inactive preparations may be explained in two ways. Many of these "ovarian residues" and "pituitary tablets" contain *desiccated thyroid* and, occasionally at least, it is the thyroid that causes the good result. Desiccated thyroid is often of value in gynecologic dysfunctions, but this is an expensive way to prescribe it. Another little realized fact which may explain these occasional good results is that many gynecologic endocrine disorders are subject to spontaneous remissions and cures. Too frequently this fact is forgotten and this pill or "hypo" receives the credit for remarkable improvement in the patient's condition.

*Estimation* of the possible value of such preparations is not difficult if a few facts are kept in mind: (1) Pituitary hormones are inactive by mouth; (2) the gonads (ovary and testis) do not store their hormones but apparently secrete

them into the blood stream as rapidly as they are formed. Several pounds of ovary or of testis must be extracted to obtain even one unit of their respective hormones. It is obvious, therefore, that one tablet of desiccated ovary can contain no biologically active amount of hormone. (3) Even if corpus luteum tablets contained progesterone, they would be valueless since progesterone is inactive by mouth. (4) The sex hormones are not water soluble; therefore, aqueous extracts of gonad material have nothing but a psychogenic value.

There is a certain aqueous extract of corpus luteum that is extensively advertised for hypodermic use. It is regrettable that certain prominent physicians, in print and in lectures, have advocated its use in cases of *threatened* or *habitual abortion*. Presumably the rationale for this treatment is based on the demonstration that this substance temporarily inhibits uterine motility. It should be pointed out, however, that inhibition of uterine motility is a very nonspecific response which could well be elicited by protein degradation products present in an extract of this type. Lack of corpus luteum function is theoretically the important etiologic factor in threatened or habitual abortion. The use of this aqueous extract to compensate for deficient corpus luteum function does not seem reasonable, inasmuch as no one has demonstrated that it actually contains progesterone or that it can cause progestational changes in the uterine endometrium.

**Active Preparations.**—FOR INTRAMUSCULAR USE.—*Estrone*, or *theelin* as it was first called, was isolated in this country. It has been widely advertised and is the most commonly used estrogen. This choice is unfortunate because estrone is a relatively inefficient preparation. Its potency per milligram is low and, relatively speaking, it is quite rapidly absorbed from the oil and excreted via the urine. This makes it necessary to inject most patients two to four times a week in order to obtain good clinical response.

Estrone and the estrone-like preparations to which these remarks also refer, are ordinarily labeled in *international units*. A commonly used dose of these preparations is the 2000 unit ampule. Sold at a comparatively moderate price, this sounds like a good buy. Actually, this is a relatively minute dose and is therapeutically equivalent to trying to relieve a headache with  $\frac{1}{2}$  grain of aspirin. Two thousand international units of estrone is equivalent to 200 *rat units*. When transposed to the human on a weight for weight basis,

this is sufficient hormone to have a minimal physiologic effect for *twelve hours only* in a woman weighing 66.6 pounds.

The *solubility* of these substances in oil is relatively low. This fact limits the amount which can be administered. I have had several menopausal patients whose symptoms could not be controlled with the maximal amounts of these substances which could be administered.

*Estradiol* is marketed in esterified forms for parenteral use, estradiol benzoate and estradiol dipropionate. These substances have several advantages over estrone and estrone-like preparations. They are more potent and are more soluble in oil. Of even greater importance is the fact that they are effective over a much longer period of time. Using these substances, the patient can be given more adequate therapy with a longer interval between treatments. This prolonged effect is most marked with *estradiol dipropionate*. In a series of fifty-five menopausal patients, we found that over half of them could be maintained symptom-free by treatment with this substance once every fourteen to twenty-eight days; the remainder needed treatment every seven to ten days. Ten of these same patients were then placed on estrone, and it was found that estrone was definitely less effective. More recently we have found that *stilbestrol dipropionate* is almost as effective as estradiol dipropionate. Stilbestrol dipropionate is not available, however, at the present time. Estradiol dipropionate is labeled in milligrams. Estradiol benzoate may be labeled in rat units, but the content is also given in milligrams.

A comparison of *estrone*, *estradiol benzoate* and *estradiol dipropionate* in terms of relative potencies per milligram is difficult. The ordinary method of comparison, *i.e.*, by rat unit assays, does not give a true index to the clinical values of these substances. The rat assay method is a short-time test for estrogenic effect and does not consider duration of the estrogenic effect. It puts a premium on rapid absorption, which is a factor that guarantees a relatively evanescent effect. Even with this method which, because of their slow absorption, penalizes them somewhat, estradiol benzoate and estradiol dipropionate are at least as potent (in terms of rat units per milligram) as estrone. In fact, most workers consider them more potent than estrone. Evaluation of the effectiveness of these substances is better shown by the following test: When 0.05 mg. of estrone is given to a castrate female rat, the vaginal estrogenic response persists for four

or five days; when the same quantity of estradiol benzoate is given, the response lasts fourteen days and, with the same amount of estradiol dipropionate, the response lasts for forty-two days.

Recommendations as to actual dosages to use in various conditions lie beyond the scope of this discussion. The most common sin in sex hormone therapy and a very common cause of poor clinical response is the use of *doses too small* to have any physiologic effect. Shorr, who has done a great deal of work on this subject, states that the usual dose necessary to produce a physiologic effect in the human female totals 6000 to 9000 rat units (divided into three doses) per week. This is equivalent to 1.0 to 1.5 mg. of estradiol benzoate or 6.0 to 9.0 mg. of estrone (60,000 to 90,000 international units). Its equivalent in estradiol dipropionate would be a little less than 1.0 to 1.5 mg. given once a week. It must be realized, however, that this is an *average* dose. The exact dose of estrogen necessary for this physiologic effect varies a great deal in different patients; some need less and frequently patients require much more.

The *actual cost* of estradiol benzoate and estradiol dipropionate, in equal *active amounts*, is less per ampule than that of estrone. The cost on a weekly or a monthly basis is greatest with estrone, less with estradiol benzoate and least with estradiol dipropionate.

No extensive discussion of the potency of androgen preparations is necessary. Only the esterified form, *testosterone propionate*, is available. This substance has a relatively prolonged effect. The more rapidly absorbed and relatively less potent free form, testosterone, is not sold. Ampules of testosterone propionate are labeled in milligrams.

There is no effective esterified form for *progesterone*. In addition to the crystalline progesterone, some relatively crude but active preparations of corpora lutea are available. One international unit of these crude extracts is equivalent to 1.0 mg. of the crystalline substance. It must be remembered that progesterone is relatively rapidly absorbed and excreted. It must, therefore, be given at frequent intervals for good results.

There are glowing reports in the literature as to the excellent therapeutic results obtained in cases of *threatened* or *habitual abortion* by treatment with  $\frac{1}{2}$  mg. or less of progesterone twice a week. It is known that in normal pregnancy 10 to 100 mg. of progesterone are produced and metabolized daily. Thus it is difficult to believe that these comparatively

minute doses have any value other than a psychogenic one. The apparent good results with this type of therapy can better be explained by the almost completely neglected fact that a good many women who might be considered "habitual aborters" or as having "threatened abortions" will have normal full-term pregnancies with no therapy at all.

The potencies of both *chorionic* and *equine gonadotropins* have recently been standardized by a committee representing the League of Nations. Ampules or vials of these preparations are now labeled in terms of these international units. This fact has improved a very confused situation. In the past the various firms used their own individual varieties of rat units. There was a variation of 300 per cent in actual potency between the various chorionic gonadotropins and 1000 per cent between the equine gonadotropins, all these substances being produced by reputable firms.

The potency of *anterior pituitary gonadotropic extracts* is not standardized. Most observers agree that products of this type have little or no value in the human. Their potency is too low and, being quite crude, their administration is too often followed by inflammatory reactions.

The *actual potency* of chorionic gonadotropin in the human is subject to much dispute. I doubt very much that it is ever clinically indicated in the human female. This substance will cause ovulation and corpus luteum formation in the rat and rabbit. Its clinical use was based on the assumption that it would have the same effect in the human. Unfortunately this is not true. All observers have been unsuccessful in attempts to demonstrate that it will produce ovulation, corpus luteum formation, or progesterone production. Good clinical results with this substance in cases of functional bleeding have been claimed by some authors and observed by some physicians. Equally poor clinical results have been claimed by other authors and observed by other physicians. If this substance were truly valuable, everyone should be able to get good results. It seems to me that the explanation for the occasional spontaneous remissions or cures in this condition lies in the relatively high frequency of good clinical results rather than in any virtue of the chorionic gonadotropin itself.

These remarks on the human potency of chorionic gonadotropin refer *only* to the female. This substance is effective in the male in that it stimulates the endocrine function of the interstitial cells of the human testis.

Dogmatic statements as to the therapeutic potency of

*equine gonadotropins* are not justified. This substance has been available for too short a time to allow an accurate estimate of its clinical value. My own experience with it is quite limited. I am convinced, however, that the clinical reports are not yet adequate to support some of the claims made for this substance. There is no doubt that it has caused the production of corpora lutea in a certain percentage of women with *normally* reacting ovaries. There is, however, scant evidence that it will cause the production of corpora lutea in the ovaries of women who are known to be sterile because of lack of ovulation. The fault in such cases may well lie in *abnormality* of the ovaries in their response to gonadotropes. It is quite possible that when the proper dosage, time and frequency of treatment are worked out, this substance may be clinically valuable. At the present time, however, it cannot be considered as the universal panacea for sterility, functional bleeding, amenorrhea and other conditions as intimated in some of the advertising for this substance.

ACTIVE PREPARATIONS FOR ORAL USE.—The remarkable oral potency of *stilbestrol* has been previously indicated. The relative inefficiency of the *natural estrogens* by the oral route has also been discussed. Oral estrogens from natural sources are being purchased and used to some extent at present. It is therefore pertinent that certain common misconceptions as to the oral potency of the various preparations should be pointed out.

*Estriol* and *emmenin* (composed, to a large extent, of *estriol glucuronide*) are widely regarded as being the most efficient oral estrogens. This is true only in a very limited and rigidly qualified sense. *Estriol glucuronide* is as potent by mouth as it is parenterally, *estriol* is a little less so, and the other natural estrogens are even less potent by mouth than parenterally. Referring then only to the effectiveness of each substance by mouth compared to its effectiveness parenterally, it is absolutely correct to say that among the natural estrogens *estriol* and *estriol glucuronide* have the greatest oral efficiency. This statement, however, has nothing to do with the actual oral potency per milligram of these natural estrogens. The very important fact that, parenterally, *estradiol* is several hundred times more potent than *estriol* and several thousand times more potent than *estriol glucuronide* has been neglected. In spite of the lower effectiveness of *estradiol* by mouth as compared to its effectiveness by parenteral administration, it is still a great deal *more potent* orally *per milligram* than is *estriol* or *estriol glucuronide*.

In giving estrogens for oral administration, *estradiol* at the present time is the substance to prescribe. Per effective amount of hormone it is the least costly to the patient.

#### SUMMARY

In general, the sex hormones available at the present time should be given by the *intramuscular* route. This method is more efficient per milligram of hormone and is least costly to the patient. Estrogens lose a high percentage of their effectiveness by the oral route. They may be given by this route, however, if the dosage requirement of the patient is low or if the cost of medication is of no consideration. For oral administration, *estradiol* is the estrogen of choice.

Estrone and estrone-like preparations are relatively inefficient by the parenteral route. *Estradiol benzoate* is more efficient and *estradiol dipropionate* most efficient. The cost of treatment is less with these latter two substances than with estrone and estrone-like preparations. *Estradiol benzoate* should be used when a relatively short effect is desired. *Estradiol dipropionate* is the drug of choice under most other conditions.

*Progesterone* has no effect by mouth. It should be given parenterally at frequent intervals. To obtain physiologic effects, doses much higher than those commonly recommended must be used.

*Pregneninolone* (anhydro-oxy-progesterone or ethynil testosterone) has been given by mouth for its progestational effects. In the experimental animal it has some effects characteristic of progesterone and other characteristic of estrogens. Its clinical use is not recommended until more is known about its effects in the human.

The only androgen that can be purchased at the present time is *testosterone propionate*. This substance is an efficient androgen when given intramuscularly. It has no practical value, however, when given by mouth.

All of the sex hormones have some clinical effect when administered percutaneously. Because of the relatively weak effect obtained by this method, *inunction* of sex hormones is not very frequently indicated.

The *gonadotropic substances* are complex protein hormones. Since they are destroyed by the digestive enzymes, they have no effect by mouth but must be given parenterally.

*Chorionic gonadotropin* does not stimulate the human ovary and it is doubtful if it is ever clinically indicated in the



female. *Equine gonadotropin* will stimulate corpus luteum formation in the female. There is little evidence that it has such an effect in women with abnormal ovarian function. It may be of more clinical value in the future when more is known about its effects in the human and when more is known about dosage and the proper time of administration.

Most workers have had poor results with gonadotropic extracts of the *anterior pituitary*. The poor results may be due to the crudity and lack of potency of such extracts.

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### THE TREATMENT OF NEPHRITIS

THE treatment of nephritis has long been difficult for the practitioner to comprehend. We will briefly review two cases of nephritis, each presenting a different aspect of the disease, in order to clarify the basic principles of therapy.

#### ACUTE GLOMERULONEPHRITIS

*Case I.*—J. B., a thirty-four-year-old white male, was in good health until three weeks prior to his admission to the Research and Educational Hospital on January 11, 1938, when he developed an acute pharyngitis. It was considered a mild infection and he kept at his work for a week, during which time he seemed to feel better. However, a week after the throat infection, he began to have vague pains in his joints, especially the ankles, and some soreness of the calf muscles. A few days later his ankles began to swell. This was fairly constant, the swelling persisting throughout the day. Later his wife noticed some swelling under his eyes and puffiness about his face and neck. He had felt quite well except for some intermittent attacks of belching, "gas" and occasional abdominal distress during the previous five years. A left herniorrhaphy had been performed in 1926 and again in 1933. Since the swelling first appeared there had been frequent watery stools; on some days as many as six movements were passed.

On examination he appeared a well developed, moderately edematous white man who was quite comfortable. His face was pale and somewhat edematous, but no suborbital edema was evident. The pharynx and pillars were injected and the tonsils atrophic. A small, barely palpable thyroid gland was present. The heart appeared normal in all respects. The blood pressure was 180 systolic and 110 diastolic. A slightly enlarged, well rounded abdomen suggested the presence of a small amount of ascitic fluid, although dullness in the flanks and a fluid wave could not be satisfactorily demonstrated. An old surgical scar was found in the left inguinal region. There was considerable edema of both ankles and legs, and there were some callosities of both knees, the result of repeated kneeling incident to his former work. He weighed 179 pounds.

Laboratory examinations assured the diagnosis of acute Bright's disease. The urine was scant in amount (400-650 cc. per day) and smoky in color. Microscopic examination revealed the presence of innumerable red blood cells, a few leukocytes, some epithelial cells, many hyaline casts, and a few finely granular casts. About 3 to 4 gm. of protein (albumin) were excreted daily.

The blood chemistry on January 14 showed an NPN. of 103 mg., urea nitrogen 67 mg., creatinine 3.2 mg., serum albumin of 2.6 gm., and a serum globulin of 1.8 gm. per 100 cc. A urea clearance test performed the following day showed only 8.38 cc. of blood cleared per minute, or 15.5 per cent of the normal renal function.

The patient was immediately put on the usual regimen for acute nephritis. This included 1000 cc. of milk and 500 cc. of cream divided into six feedings, supplemented by daily intramuscular injections of 0.2 gm. ascorbic acid and 15 grains of sulfanilamide every four hours. This provided 1675 calories. There was a gradual daily improvement so that, after ten days, he had lost considerable edema. His weight fell from 179 to 161 pounds. The urine showed fewer red blood cells, only a few granular casts, and the protein excretion fell to 2 gm. daily. As his initial diet was considerably under his basal requirements (1800 calories), two eggs and 10 gm. of sugar were added to bring it up to the needed value. It gave four feedings and two egg-nogs, thus relieving the monotony of the original diet.

Improvement continued during the next two weeks. The blood pressure fell to 132/84; there were fewer red blood cells in the urine and the patient's weight was 142 on February 4. The NPN. had fallen to 78 mg., the urea nitrogen to 50 mg. and the creatinine to 2.6 mg. per 100 cc. By the fourteenth of the month he weighed 134½ pounds, or a loss of 44½ pounds in five weeks. Thirty per cent more calories was added to the diet. This new diet consisted largely of toast, cereals, baked potatoes, butter, and orange juice. It contained 131 gm. of carbohydrate, 187 gm. of fat and 70 gm. of protein, providing 2475 calories daily. Vitamin C tablets, 25 mg., and vitamin B-G syrup in teaspoonful doses, were given thrice daily. Improvement was still taking place.

On February 23, this was considered a fairly well healed case of acute glomerulonephritis. The urine contained no casts, and occasionally 4 to 6 red blood cells per high power field could be seen in the centrifuged specimens. The blood chemistry had returned to normal (NPN. 20 mg., urea N 12 mg., and creatinine 1.9 mg. per 100 cc.). To compensate for the small daily proteinuria, 0.3 to 0.5 gm., he was put on a diet of 124 gm. protein, 175 gm. carbohydrate, and 142 gm. of fat. He gained some weight and felt better, although the diet did not change his urinary sediment excretion nor diminish the proteinuria. He was discharged from the hospital on March 24 as a latent case of glomerulonephritis. At no time did he have dyspnea, palpitation, tachycardia, or cardiac distress.

The patient then returned to the dispensary and, during the next year, there was a gradual diminution in the proteinuria. The blood pressure, blood chemistry and urinary sediment were normal. He was discharged from the clinic in September, 1939, as a healed case of acute glomerulonephritis.

**Treatment.**—In acute glomerulonephritis the physician is faced with badly damaged kidneys. A majority of the filtering units of the kidney are clogged by the products of acute inflammation. At this stage of the disease their effectiveness is reduced to nothing, and consequently very little urine is manufactured. The little that is formed contains a great deal of albumin, casts, red blood cells and nitrogenous wastes. In time, the products of inflammation are absorbed and the filtering units are able to perform their normal duties. The chief concern of the physician is therefore to *assist the natural re-*

*parative process*, maintain an adequate *water balance*, provide sufficient *nutrition*, and obtain skillful *nursing care*.

*Rest* is the most important factor in the treatment of Bright's disease. The patient should be given complete bed rest as soon as the disease is diagnosed or even suspected. This period of rest should continue until all signs of red blood cells disappear from the urine. Usually this requires six to ten weeks of complete bed rest. In some cases the urinary sediment may clear up quickly but mild amounts of proteinuria may still continue. Such patients are allowed some activity after the second month; if this does not increase the hematuria, they are allowed more activity by the end of the third month. It is during this early period that close clinical watch of the patient and skillful nursing care are imperative, so that complications may be avoided. If they occur they are quickly recognized.

Acute glomerulonephritis is a self-limited disease, and the medical management of these cases is largely *dietetic*.

Volhard and Fahr were so intent on resting the kidney during the acute phase of the disease that they advocated a *hunger-thirst regimen*. All food and fluid were withheld for three to five days. Later they modified this plan by allowing some fruit juice, a few crackers, or a cup of weak tea. It was assumed that this procedure completely rested the kidneys. There are two objections to the Volhard thirst management. In the first place the patient is constantly losing water through his breath, through his skin and through his bowels. To compensate for these water losses a patient on the hunger-thirst regimen must draw on his body store of water. The dangers of dehydration are added to the disease. In the second place, the fever and starvation lead to acidosis. Consequently, this plan does not put the kidneys completely at rest.

An ideal method of treatment would be one that provides sufficient fluid to make good the daily losses through the breath, bowels, and skin, and one that would forestall hunger acidosis. A modification of the *Karell diet*, such as was given the patient in Case I, fulfills these requirements. There were 1500 cc. of fluid and 1675 calories given daily. The latter value is considerably less than the patient's caloric needs, but this offers no serious objection since it is given only during the first week of the disease. Later it can be raised to the full caloric needs. This is done by increasing the *carbohydrate* content of the diet. This includes: fruit juices, cooked vegetables except rice, corn, green peas or lima beans, fresh or

cooked fruits, oatmeal, tapioca or arrowroot puddings, baked potato, clear jelly, honey, sugar, and cream. Glucose gives ready calories and helps in the oxidation of fats. Body proteins are not burned to as great an extent, hence glucose really is a protein sparer.

Some objection might be raised to the milk and cream diet as it contains protein and sodium chloride. We have not seen any harmful effects from its use; in fact, recovery took place more rapidly by this method of therapy. There is experimental evidence that neither proteins nor salt retard the healing of acute glomerulonephritis.

*Diuretics* are rarely needed. Spontaneous diuresis usually begins after five days. After that the fluid intake is largely governed by the output. Mercurial diuretics should never be given because of the harmful effects on the inflamed kidney tissue. On three occasions we have observed patients with acute glomerulonephritis who were given intravenous injections of mercurial diuretics prior to their entrance into Research and Educational Hospital. In none of them did it produce diuresis; in fact, their acute illness was considerably more prolonged. Fortunately all of them eventually recovered from this ill chosen form of treatment.

A few other considerations are of importance. As these early diets are lacking in *vitamins* B, C and G, it has been our practice to supplement these factors. During the first few days ascorbic acid (0.1–0.2 gm.), once or twice daily, is administered parenterally. After diuresis sets in all vitamins are given by mouth. The 25-mg. ascorbic acid tablets and the syrup of B and G have worked well. Occasionally laxatives are needed. Mineral oil, cascara sagrada, or milk of magnesia are the ones of choice.

*Sulfanilamide* in doses of 1 to 2 gm. three times to four times daily has given excellent results. It is apparently most helpful in cases where there are active foci of streptococci. The drug was very effective whenever there were organisms free or circulating through the body. When there were no longer active foci and the patients had passed to the secondary or allergic stage of the disease, sulfanilamide was of no value.

A majority of patients with acute glomerulonephritis recover spontaneously, but there are two complications that are often fatal: They are *cardiac failure* and *acute pseudo-uremia*. In general, patients with an acute nephritis have a bradycardia. A pulse rate of more than 80, dyspnea, orthopnea, palpitation, extrasystoles and electrocardiographic changes are

indications of cardiac failure. Digitalis in full therapeutic doses must be given as soon as any of these signs appear.

*Acute pseudo-uremia* is the other important complication. It is characterized by headache, apathy, vomiting, amaurosis and coma. As it is not related to the absolute retention of nitrogenous waste products in the blood stream it is not uremia. Instead, it is the result of an acute edema of the brain—and hence is more properly referred to as acute pseudo-uremia—and is by no means a hopeless condition. At the first appearance of headache, apathy, or spots before the eyes, 30 to 60 cc. of a 50 per cent solution of magnesium sulfate should be given by mouth. This may be repeated every four hours until a fall in blood pressure is obtained. If coma or convulsions supervene, more energetic methods must be used. Any of the recently introduced dehydrating agents work admirably. We have found 50 cc. of 50 per cent sucrose given intravenously entirely satisfactory. It may be repeated in four or six hours, although one or two injections are usually sufficient. There have been some reports of tubular degeneration following the use of these agents. The brilliant results in relieving convulsions or coma of acute pseudo-uremia by these agents justify the risk of tubular degeneration. Moreover, there is evidence to show that this tubular degeneration is transient and heals in a comparatively short period of time while untreated acute pseudo-uremia is speedily fatal.

**Summary.**—In acute glomerulonephritis, the physician is faced with badly damaged filters or nephrons. In time the natural reparative processes will remove the products of inflammation so that function can return to normal. It is essential that the physician give *adequate fluid*, provide *sufficient nutrition*, watch for *complications*, and have skillful *nursing care* in all cases of acute nephritis.

#### NEPHROSIS AND THE NEPHROTIC SYNDROME OF GLOMERULONEPHRITIS

**Case II.**—M. R., a nineteen-year-old white girl, entered the hospital on December 31, 1937, complaining of swelling of the ankles and thighs. She had been well until ten months prior to admission when she began to have a gradually increasing swelling of her ankles and thighs. As this made it difficult for her to walk, she consulted a physician who found albumin and casts in her urine and advised her to stay in bed. A special diet of fruit juice and milk was given for a week. Then she was given ammonium chloride and an injection of salyrgan and the edema decreased slightly. In August, 1937, the edema had become so great that she could hardly move. Some pain was felt in the right hip. It was said that there was less albumin in her urine. She was given a high protein diet of meat, fish, and eggs, which made her feel somewhat

better. A rash appeared over her chest and back, there was some wheezing bronchitis, and a few days later she became quite swollen. This bout subsided in a week, only to recur at monthly intervals for the next three months. Skin tests failed to reveal any clue of the exciting factor of these reactions. There was no history of frequent sore throats, scarlet fever, or sinusitis. Amenorrhea had been present for three months prior to admission.

Physical examination revealed a poorly nourished girl whose face was very puffy and edematous. Her pupils were round, equal, and reacted to light and accommodations. The conjunctival and mucous membranes were pale. The tonsils had been removed and the pharynx was injected. Excursion of the chest was limited, particularly over the bases. Tactile fremitus was impaired, the percussion note dull, and the breath sounds inaudible over these regions. In the upper portions of the lungs many dry crackling rales and squeaks were heard. Her heart was normal in all respects, and the blood pressure was 126/90. Her abdomen was greatly enlarged and a fluid wave was easily demonstrable. There was marked pitting edema of her extremities.

The laboratory examinations showed the following: in the urine, some granular casts, many red and white blood cells, and a heavy reaction of albumin; cholesterol 500 mg., serum albumin 1.19, and serum globulin 1.97 gm. per 100 cc. The basal metabolic rate was normal, as were all other values.

The patient was given a high protein, salt poor diet and frequent blood transfusions. Her diet contained considerable meat, fish, fowl, and milk, consisting of a daily intake of 110 gm. of protein, 88 gm. of fat, and 170 gm. of carbohydrate—or a total of 1900 calories. In addition 0.2 gm. of ascorbic acid was given daily. Blood transfusions of 350 to 355 cc. of whole blood gave her the most relief from her edema. Twelve transfusions were given during the first four months of her hospital stay. They did not materially increase her circulating blood protein values, but they greatly reduced her edema and made her more comfortable. One could not help but be impressed by the great relief that she would get during the two to five days after a transfusion. Usually there would be a fairly good diuresis the day of the transfusion, and a weight loss of 2 to 8 pounds was not uncommon. During the next few days there was a gradual reaccumulation of fluid, necessitating an additional transfusion.

Since the outstanding symptom of this disease is due to the lowered serum proteins, various means were tried to raise these values: On April 29, 500 cc. of a 6 per cent acacia solution was tried, but she developed an urticarial rash. Four days later 100 cc. of a 30 per cent aqueous solution of acacia was given intravenously, slowly, and she lost 2 pounds of edema fluid. Several other injections were given with similar results. Early in July, without any apparent reason she had a spontaneous diuresis and lost 16 pounds of fluid. By the end of September she had slowly gained enough fluid to be as edematous as on admission to the hospital. A 5 per cent solution of amino acids in dextrose was given on several occasions and this was followed by slight diuresis. She improved sufficiently so that she was discharged from the hospital on November 23, 1938.

After that her edema cleared and there was continued improvement until her readmission on March 7, 1939. At that time there was no edema of the extremities and her blood pressure was 125/85. The urea clearance was 23.4 cc., or 43 per cent of the normal value. She was able to concentrate urine to 1.016 and the intravenous phenolsulfonphthalein showed only a 10 per cent return of the dye after fifteen minutes. All of these tests indicated a definitely impaired renal function. Daily albuminuria of 1.0 to 12.8 gm. was noted. Blood cholesterol values were 615-625, the serum albumin 2.16, and serum

globulin 2.09 gm. per 100 cc., and the nitrogenous waste products were all of normal values. A sternal puncture showed a normocytic anemia with a shift to the left. The increased sedimentation rate (38 mm. per hour) suggested a toxic process. As she felt well and had no symptoms she was discharged from the hospital on April 3, 1939.

During the last week of May she contracted a head cold that precipitated another bout of edema, so she returned to the hospital on June 1, 1939. An examination at that time disclosed a slight amount of edema and the retinal vessels were normal. She was given complete bed rest and a high protein, salt-free diet. Some facial and ankle edema recurred, so she was given several transfusions. A proteinuria of 8.0 gm. per day persisted. At that time nitrogen retention first appeared (NPN. 42 to 59 mg., urea N 27.6 mg.). The urea clearance had fallen to 13.0 cc. per minute, or 24 per cent of normal. Following the transfusions the patient had improved sufficiently to allow her to go home, on August 21, 1939. A diet of 60 gm. of protein, 100 gm. of fat, and 181 gm. of carbohydrate was given.

While at home she had several cycles of edema and edema-free periods, but finally the edema increased to such an extent that she was readmitted to the hospital on January 29, 1940. Examination at that time revealed a blood pressure of 148/108; otherwise there was no change. The fundi showed no pathologic changes. The laboratory findings were most significant: the NPN had risen to 66.7, the urea N to 51.3, the creatinine to 4.2, and the cholesterol to 600 mg. In April, the urea clearance fell to 9.6 cc. per minute, or 18 per cent.

When seen in the dispensary on July 19, there was some dyspnea on exertion and a moderate amount of edema of the body and legs. The NPN had risen to 86.7, the urea nitrogen was 36.4 and the creatinine was 5.7 mg. per 100 cc. Her cholesterol still remained high (590), but the serum albumin was 3.3 and the serum globulin 2.2 gm. The blood pressure 136/94.

A tentative diagnosis of nephrosis was made early in January, in this case on the basis of the insidious onset, the massive edema, the heavy proteinuria, the low serum protein values, the high cholesterol and the normal blood pressure. A differential diagnosis between a true lipoid nephrosis and the nephrotic syndrome of glomerulonephritis would include the features outlined in the accompanying tabulation.

A urea clearance test on January 13 showed 26.2 cc. of blood cleared per minute, or 48.5 per cent of the normal renal function. This finding, in addition to the occasional demonstration of 2 to 10 red blood cells per high power field of centrifuged urine, leads us to change the diagnosis to that of the *nephrotic syndrome of glomerulonephritis*.

The term "nephrosis" was first introduced in the literature to denote a purely degenerative lesion. It is a bilateral non-suppurative lesion of the kidneys characterized by heavy proteinuria, edema, and the presence of doubly refractile bodies in the urine of patients without any elevation of blood pressure, without any red blood cells in the urine, alteration of



## TABULATION

## DIFFERENTIAL FEATURES OF TRUE LIPOID NEPHROSIS AND THE NEPHROTIC SYNDROME OF GLOMERULONEPHRITIS

	Nephrosis.	Nephrotic syndrome of glomerulonephritis.
Onset.....	Insidious	Usually follows a sore throat, tonsillitis, sinusitis, or upper air passage infection
Blood pressure.....	Normal	Elevated
Edema.....	Massive	Massive
Retinal vessels.....	Normal	May show some exudative changes
Heart.....	Normal	May show EKG changes
Urine:		
Red blood cells.....	Absent	Present early in the disease
Albumin.....	Large amounts	Large amounts
Concentration tests...	Normal	Impaired
Blood Chemistry:		
NPN.....	Normal	Elevated
Cholesterol.....	High	Normal or may be elevated
Urea clearance.....	Normal	Impaired
PSP test.....	Normal	Impaired
Concentrating ability...	Normal	Impaired
Basal metabolic rate...	Low	Normal
Prognosis.....	Good, except for intercurrent infections	Poor
Course.....	Prolonged with few renal changes. Many heal	Gradual loss of renal sufficiency, all eventually succumb

the retinal vessels, or enlargement of the heart, and without renal insufficiency as evidenced by a normal nitrogen excretion and a normal dye excretion. By "no hematuria" is meant not more than 2 to 4 red blood cells per high power field of centrifuged urine specimens.

The *cause* of nephrosis is unknown. In most cases it begins without any apparent reason. Insidiously edema begins, later to become more and more evident despite the fact that a careful history failed to reveal any antecedent infection or illness. These cases have been called "genuine" by Volhard and Fahr, and more aptly "cryptic" by Addis. There are other cases which have been said to follow or to have been casually related to an odd assortment of causes, as chronic infection, heavy metals, or disturbances of metabolism. Specifically, osteomyelitis, chronic suppuration, tuberculosis, syphilis, mercury, gold, arsenic, diabetes mellitus, and the toxemias of pregnancy have been advanced as causes of nephrosis.

**Symptoms.**—The symptomatology of the disease is striking: *Albuminuria* is always present and may be as great as

30 gm. per day. Usually it is much less, and very frequently chronic. A typically soft *edema* of the tissues of the face and neck on first inspection often suggests the diagnosis. It is first apparent in the lax tissue of the eyelids, and is worse in the morning and better as the day wears on. *Ascites*, *hydrothorax* and *anasarca* follow and may be so great as to mark the true loss of body flesh of the patients. *Urinary changes* are determined by the edema. With the formation of edema there is oliguria; with loss of edema, polyuria. When the edema is immobile, the daily urinary volume is unchanged. Apparently there is no vascular reaction, as the blood pressure, retinal vessels, and cardiac size are unchanged.

The *nephrotic stage of glomerulonephritis* is characterized by the persistence of signs of active renal destruction. At times this may be so gradual that it is confused with true nephrosis. Later there is progression of the disease to a certain point, after which it appears inactive; however, the patient gradually loses some of his renal functions. Usually there is a mild to a heavy proteinuria recorded as a + to ++++ (0.5 to 20 gm. or more of protein per day). As a result of this proteinuria, the serum proteins are low. If the serum albumin is below 2.0 and the serum globulin less than 1.5 gm. per 100 cc., the patient is likely to have edema. Often there is slight nitrogen retention with corresponding elevation of blood nitrogen values. Unless there is a history of any of the following: a previous acute attack, persistent hematuria, some elevation of blood pressure, diminution of urea clearance, loss of concentrating ability of the kidneys or nitrogen retention, the diagnosis of the nephrotic syndrome of glomerulonephritis is not easily made. There are cases that present the nephrotic state without any signs of active nephritis, and the differential diagnosis between a nephrosis and the true condition is impossible. To these cases Volhard has given the name "nephrotic type of glomerulonephritis," while Osler referred to the condition as "chronic parenchymatous nephritis." Failure to observe these cases over a long enough period of time, as well as incomplete studies of them has been responsible for some of the misleading statements that appear in the literature to further confuse the picture.

Differentiation between the *hemorrhagic* disease and pure nephrosis is usually made by the presence of three important characteristics: hypertension, nitrogen retention, and hematuria, either singly or in combination. Some patients have less of the angiospastic reaction than others so hypertension may

be absent in them. Nitrogen retention is also an equivocal sign, since it may not be present until fairly late in the disease. In well compensated renal insufficiency it may be evident only by urea clearance tests. On the other hand, the degenerative processes of nephrosis may extend to such a degree that there is a material reduction in the number of functioning nephrons. In those cases there will be an impairment of urea clearance, followed later by nitrogen retention. Hematuria is the most important sign. It may be intermittent or a dry diet may be needed to make it apparent. When present, nephrosis can be definitely excluded. A definite history of an acute Bright's disease with hematuria is of equal diagnostic import.

The importance of separating these two entities lies in their different prognoses. The nephrotic syndrome of glomerulonephritis always leads to a terminal stage, usually uremia and death. Nephrosis is more likely to lead to recovery, or death by a pneumococcal infection. A few patients with nephrosis are said to die in uremia.

Usually there are signs of *renal impairment* in the nephrotic syndrome of glomerulonephritis. The sensitive urea clearance test generally shows some impairment, as in Case II. Hematuria is very commonly still present from the acute or initial attack. If after four months of the original attack of acute nephritis improvement does not begin, the patient passes into the active chronic or terminal stages of the disease. The hematuria is not necessarily great, for there are some cases in which a special twelve-hour dry diet is needed to make it evident on microscopic examination. With time, however, the hematuria, like the concentrating ability of the kidneys and the urea clearance, gets worse. In a few instances it is believed to remain stationary but not for long. It is indeed exceptional that these patients improve sufficiently to pass to the latent stage.

The life span of a patient with the nephrotic syndrome of glomerulonephritis varies from several months to several years. There are a few cases that pass directly from the acute attack to the terminal stage. A majority of the patients will die within three to five years after the initial attack.

*Edema* follows the loss of the circulating serum proteins. When animals are bled daily and thereby deprived of their serum proteins (plasmaphoresis), edema ensues. These experiments emphasize several points: First, the bleedings must be daily and for several weeks before the circulating serum proteins are reduced. This means the body possesses a large factor of safety before it exhibits any change. These experi-

ments also provide a method of studying the manufacture of these proteins. Serum albumin is readily manufactured at first; serum globulin at a much slower rate. After some weeks the serum albumin production drops considerably but the serum globulin continues at nearly the same rate. Still later both are depressed and are formed at slow rates of speed. Edema appears when the total circulating proteins are below 2.5 per cent. Since serum albumin exerts about four times the osmotic force of serum globulin, it is evident that a drop in the former is the more serious of the two. Considerable attention has been attached to the *serum albumin and serum globulin ratio*. Normally it is about 1.5 to 2.5. In nephrosis, for reasons given above, it becomes reversed, so that there is more globulin than albumin, or ratio of 0.5 to 1 is seen. Much stress has been laid on this reversal of the A/G ratio. Without denying its existence it has focused attention on the wrong thing. Of the constituents of the blood serum, albumin exerts the greatest osmotic force. Since the greatest portion of osmotic pressure comes from the serum albumin, the real emphasis should be on: (1) total osmotic pressure and (2) its chief active agent, serum albumin.

**Treatment.**—A differential diagnosis between lipoid nephrosis and the nephrotic syndrome of glomerulonephritis is of little importance concerning treatment as long as renal sufficiency is present. These two conditions present nearly identical clinical pictures and in both the main therapeutic effort is directed toward the riddance of edema.

Edema is the stumbling block for the physician. One of the main objects of treatment is to elevate the lowered serum albumin and globulin by feeding *high protein diets*. Theoretically this appears to be simple replacement therapy: merely feed enough protein to make good the urinary losses. In practice, however, such quick results are rarely observed, as was well illustrated by Case II. High protein diets are an important feature in treatment. In our experience we have used diets of 90 to 120 gm. of protein daily. These are about the highest amounts that patients will take over a long period of time. Considerable ingenuity is needed to make a patient contented to stay on this type of diet. Usually meat, fish, fowl, and milk are offered. There seems to be no doubt that meat, and particularly thick steaks and roast beef, are the most effective means of raising the serum proteins. Further, patients do not tire of meat diets as quickly as they do of cereal diets. In order to have sufficient protein from vegetable sources alone, so much bulk and roughage must be added that

the lower bowel is quite irritated and gastro-intestinal problems arise. Thus for all practical purposes the chief dietary reliance in nephrosis is on a heavy meat diet. As long as the nitrogenous waste products are cleared from the blood stream such diets cause no irritation to the kidneys.

In periods of stress, high protein diets must be supplemented by other means. *Blood transfusions* are really serum protein replacements. It has been our experience that transfusions of 400 to 500 cc. of whole blood are of inestimable value. It is true that a single transfusion does not raise the serum albumin and serum globulin values much. The subjective relief, the diminution of edema and the restored sense of well-being of the patient after a transfusion are impressive. As the effects of a single transfusion last only several days, it must be repeated frequently. This is especially true whenever the edema is great enough to cause dyspnea. It has been our policy to follow the rule of "when in doubt, transfuse." Undoubtedly, the use of pooled serum and lyophile serum will be much more extensive as they become more generally available. While the intravenous injections of acacia and amino acids have given some promising results, they are not recommended for general use.

*Salt-poor diets* must be used during the entire course of treatment. It is well known that sodium chloride attracts more fluid in the tissues, hence its intake must be limited.

A number of other methods of treatments have been suggested from time to time. *Thyroid extract* has been given because many patients have a low basal metabolic rate. We have given it almost routinely in  $\frac{1}{2}$  grain doses three or four times daily, but have not seen any beneficial effects. *Acid diuretics* like ammonium nitrate and ammonium chloride have been used, but they do not reduce the edema. Some have reported excellent results from the removal of purulent foci, but we cannot be as enthusiastic. Obviously, all *septic foci* should be removed and this has been our practice.

Elevation of the blood nonprotein nitrogen, urea nitrogen and creatinine values means the beginning of *renal insufficiency*. At this stage the patient cannot completely rid his blood stream of waste products. The treatment of this condition is a distinct problem from that of edema.

**Summary.**—The treatment of nephrosis and the nephrotic syndrome of chronic glomerulonephritis is the treatment of edema. *High protein, salt-free diets* are most important. In periods of stress, *transfusions* are most helpful and must be frequently repeated.

## CLINIC OF DR. FREDERICK REHM SCHMIDT

FROM THE NORTHWESTERN UNIVERSITY MEDICAL SCHOOL  
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### TREATMENT OF COMMON SKIN DISEASES

THE correct treatment of diseases of the skin is dependent upon knowledge of the physical, chemical and biologic status of the normal skin. Investigations of the last few years have contributed much to an understanding of this complex problem.

#### DERMATITIS AND ECZEMA IN ADULTS

We have learned, for example, that the normal reaction of the unbroken skin is acid, varying between a hydrogen ion concentration of 4 and 6. When inflammation occurs and the continuity of the cutaneous surface is broken, a definite alkaline reaction sets in. Erythema is followed by vesiculation. The vesicles break and exudation takes place, with subsequent formation of crusts. This is the picture of the most common disorders of the skin, dermatitis and eczema, which for the purpose of this clinic are considered as one and the same type of cutaneous response, from whatever cause.

The efficacy of applications of solutions of boric acid and aluminum acetate is thus explained on a sound basis. The alkaline reaction of the oozing surfaces is neutralized by acid solutions, thus aiding epithelization to proceed normally. Weeping stops and new skin forms.

Affected areas should be wrapped in cheesecloth or gauze and kept wet with one of the following preparations:

*Saturated solutions of boric acid* are usually employed hot. The heat may be retained by covering the gauze with oiled silk or waxed paper. *Solution of aluminum acetate, N.F.*, on the other hand, is best used cold. One tablespoonful of this in a pint of cold water is usually well tolerated. Compresses of this nature must be kept wet, otherwise they are detrimental.

The compresses should be removed at night. A mild

astringent lotion is then applied. An efficient preparation of this kind is *calamine lotion*, N.F. The full strength lotion often causes "caking." Serum cannot escape, so that secretions are as effectively dammed up as if an ointment were applied. It is therefore advisable to dilute the lotion with an equal part of distilled water.

The use of a diluted calamine lotion brings up the question of *topical medication* in dermatotherapy. Excessively strong remedies are constantly being prescribed. Best results are obtained with *mild, soothing* applications.

The choice of drugs should not be difficult because a very few suffice to treat all diseases of the skin. These are listed in the U. S. Pharmacopoeia and National Formulary. Every druggist has them on his shelves. They are efficient and economical. Vaseline may be added to an official ointment to secure the desired strength of its active ingredient. It is always best to begin the management of a dermatosis with a weak dilution or concentration of your favorite prescription.

The necessity for this admonition is demonstrated in the clinic only too frequently by the results seen following the administration by the patient or his physician of ammoniated mercury ointment, U.S.P., which contains 10 per cent of ammoniated mercury. A generalized dermatitis may be caused by the application of this commonly used mercurial preparation to a small area of skin. A severe toxic state may ensue, with grave consequences. It is best to make a patch test with a 3 per cent ointment before prescribing it in greater strengths.

*Case I.*—The man before us has weeping dermatitis of the hands and forearms. He has been told to apply cold compresses of a solution of aluminum acetate. We will suppose that he goes home and does this for a few hours a day. But the rest of the day he is working at his trade of mixing cement. Cement has caused the trouble and now it continues to aggravate it. He has failed to comply with the first and most essential principle of the treatment of eczema and dermatitis—removal of the cause. He will probably return to us in a few days with a generalized dermatitis. Wet dressings will then be impracticable and positively dangerous because of chilling.

It is in just these cases that the *prolonged bath* is of great benefit. A bathtub especially constructed to permit a patient to remain in it for twenty-four hours of the day has been installed in this hospital. A patient beset by itching and messy salves and lotions usually finds relief in the water. A little boric acid is added to insure acidity. The patient's stay in the tub is gradually increased, until he is allowed to remain as long as he wishes. No soap is used. Individuals with a dry

skin should not remain in the water more than a short time at first.

All exudation having stopped, a change is made to *ointments, pastes or oily suspensions*. Therapy is now directed toward the restoration of a normal skin as quickly as possible. The new epidermis that is forming should be strengthened. This is accomplished by the use of such keratoplastic drugs as ichthyol, sulfur, mercury, crude coal tar and resorcin. Drugs of this class also act as reducing agents, eliminating the scales which always follow in the wake of acute dermatitis. An efficient remedy in dry, scaling dermatitis is afforded by incorporating from 2 to 5 per cent of one of these drugs in zinc oxide ointment, U.S.P. But the cost and the danger of absorption of toxic quantities in treating large areas of skin with an ointment make the use of a lotion preferable. Such a lotion is made by adding a few grams of bismuth subnitrate and zinc oxide to equal parts of lime water and olive oil.

Dietary restrictions are advisable in extensive cases of dermatitis. The intake of fluids and salt should be limited. Large doses of sodium bromide in cinnamon water, given at the onset of an attack, are helpful. Intravenous injections of sodium thiosulfate or calcium thiosulfate are often beneficial. The solution of sodium thiosulfate should be freshly prepared.

*Roentgen therapy* is often of great value in subacute and chronic eczema. Hypertrophic, thickened patches grow soft after a few treatments. Acute eczema and dermatitis should not be exposed to roentgen rays.

**Occupational Dermatitis.**—Dermatitis due to contact with substances to which a worker is exposed in his occupation is now compensable in many states of the Union. The detection of the irritant is often difficult because of the complex chemical compounds used in industry. Installation of clean methods of manufacture has reduced the number of such cases.

*Prevention* of occupational dermatoses is possible. Persons in contact with irritating dust should not use greasy creams. Greaseless creams may be used as a protection against petroleum and lubricating oils, and a lotion containing equal parts of boric acid and alcohol applied before and after work. Workers exposed to irritants should be taught how to cleanse their hands.

The use of patch tests prior to employment, in an effort to eliminate those applicants susceptible to dermatitis, is not feasible. Young untrained workers are most susceptible.

Hospitalization of patients is frequently necessary. Roent-



gen therapy should not be employed unless one is certain that the patient is not a malingerer. Secondary infections may be treated with autogenous vaccines.

Some cases defy all attempts at cure. Here the promise of a lump sum in compensation often has a magical effect.

#### ECZEMA IN INFANTS AND YOUNG CHILDREN

The cooperation of the mother is of paramount importance in treating infants and young children afflicted with this disease. Eczema in these little patients constitutes one of the most difficult chapters in cutaneous therapy. Failures and disappointments are frequent.

The commonest type of infantile eczema is presented by the baby with red, swollen cheeks covered with crusts. There may be patches of dermatitis on other parts of the body. Vesiculation and exudation are present. This form usually begins in the first few months of life.

The other type of eczema seen most frequently begins a little later in the first year. This may be preceded by exudation. The secretions disappear and the child acquires patches of dry, scaling skin interspersed with papules. The skin elsewhere is also often dry. These children are candidates for atopic dermatitis and have trouble with their skin throughout life.

The mother is often driven to desperation by the unsightly appearance of her child. He scratches himself constantly. A few words of assurance to the mother will help to allay her fears of damage to the child's health from lack of sleep. Eczema does not leave scars and the mother should be told this. (Letting grandmother have the child for a few weeks sometimes does wonders!)

Having brought as much order and quiet to the home as possible, the next thing to do is find out what factor or factors in the environment were new at the time of onset of the skin trouble. Had codliver oil or orange juice been added to the diet at that time? Was baby playing with a freshly lacquered toy? Had a dog joined the family? The possibility of contact with an irritant should be kept in mind.

The elimination of an *allergen* such as orange juice or wheat occasionally results in improvement. However, if scratch tests show sensitivity to egg white, omitting eggs from the diet does not influence the eczema. The child may grow violently ill after eating eggs, but the eczema does not grow worse. Sensitization to egg is merely an indication of allergy,

and is not the cause of the eczema. Hypersensitivity to egg and eczema are probably separate manifestations of a congenital idiosyncrasy.

Washing with certain *soaps* is allowed. A weeping skin is slightly alkaline in reaction and we have recently learned that such a skin possesses a lessened resistance to alkalis. Acidulated soaps of sulfonated oils are now on the market and are well tolerated by most people with sensitive skins. In lieu of such soaps, the following procedure is often of value: The child is first scrubbed with ordinary soap, leaving the lather on the skin for several minutes. This is removed with cold water. After drying, a 5 per cent aqueous solution of tannic acid is daubed on lightly. Borated talc is then dusted on the lesions to prevent the linen from staining. This sequence is repeated several times daily. The exudation tends to stop, and the child is comfortable for several hours after each treatment.

Eczematous patches may be covered with *zinc paste* containing from 15 to 25 per cent of pure (not synthetic) naphthalan. *Crude coal tar* may be used instead, beginning with a concentration of 3 per cent and increasing this as improvement sets in.

A child that is covered from head to foot with weeping, crusting dermatitis does well in the bathtub. Itching stops and crusts are washed away. Epithelization is hastened by adding a little boric acid to the water.

#### ATOPIC DERMATITIS

The child whose dermatitis begins with dry, scaling areas of inflammation often has parents who have hay fever, asthma or urticaria. He may develop hay fever or asthma later in life. Throughout the years of adolescence he may have several attacks of itching dermatitis that leave their imprint on the skin. These brownish, lichenified areas of neurodermatitis are characteristically located in the bend of the elbows, sides of the neck and around the eyes.

Persons suffering from this disease are greatly to be pitied, because as yet no remedy has been found to cure it. A change of climate often benefits these patients, solely because they are removed from a harmful environment. A nagging, neurotic mother may be a precipitating factor in bringing on an attack of itching. Or it may be house dust.

During an exacerbation of the disease, most patients obtain a maximum degree of relief from the application of cold, wet

dressings made of a solution of *aluminum acetate*. When the attack has subsided, a weak ointment of crude coal tar may be used on the patches of thickened skin.

The patient should be helped in securing as much mental and physical *relaxation* as is possible under the circumstances of his life. Short rest periods during the day are indicated. The quieting effect of warm baths is beneficial, provided that his skin is not too dry. The precocious, nervous child should be restricted in his mental and physical activities. An attempt must be made to ease the financial, marital or familial burden under which the patient is suffering.

In those individuals exhibiting a positive reaction to the intradermal injection of minute amounts of house dust or fungi of the *Trichophyton* and *Alternaria*—*Hormodendrum*—*Penicillium* group, considerable benefit may be anticipated from the use of *vaccines* made from these substances. This is especially true of those patients showing a strong reaction to the dust collected in a vacuum cleaner in their own homes. Desensitization to animal dander and pollens has not proved successful in my experience.

In a small group of such cases the administration of small doses of *thyroid extract* produces striking improvement. The skin appears to soften and the itching diminishes.

#### ACNE

Acne is a disease whose social and economic aspects are of vast importance. An unsightly complexion bars many people from employment of various kinds. The social adjustment of a person to his environment is made difficult by blemishes on his face.

Since we are still ignorant of the cause of acne, it follows that any disturbance of the internal organs should be overcome on the theory that thus we are eliminating a possible etiologic factor. Gross errors of diet and hygiene, as well as irregularities of elimination and menstruation, should be corrected.

Many young patients are drinking too much milk. A few months ago a boy of seventeen consulted me about his acne, which was of a severe grade. He said that he had been drinking three quarts of milk daily, in addition to a full diet of other foodstuffs. His mother wondered whether he was eating enough. A reduction to a pint of milk a day with prohibition of chocolate, nuts and peanut butter has greatly improved the condition of his face.

The anemia of young women may be banished with adequate doses of tablets of *ferrous sulfate*. *Vitamin therapy*, although carried to the limit of the patient's pocketbook, has not proved of lasting benefit in my experience.

Patients should indulge in a reasonable amount of outdoor *exercise*. Showers in the morning before going to work are recommended, in conjunction with abdominal massage which the patient can carry out himself. Correct posture is equally essential.

Persons with seborrhea and acne should wash their faces two or three times daily with a neutral soap which they have learned does not irritate their skin. Vigorous rubbing with a washcloth or complexion brush must be avoided. The lather is allowed to remain on the face for a few minutes before it is washed off with cold water.

The nightly application of a solution of *borax* to the face is advisable. The keratolytic action of borax serves to remove the scale that plugs the openings of the sebaceous glands. It allows the skin to breathe again, so to say. The patient is told to begin using  $\frac{1}{2}$  teaspoonful of borax in a pint of hot water. This is applied and the face dried.

A small amount of a *sulfur* lotion is then patted on the face and allowed to remain over night. The use of colloidal aluminum silicate (*bentonite*) provides a better vehicle for suspension of sulfur than does lime water.

R	Precipitated sulfur . . . . .	7.0 gm.
	Camphor . . . . .	0.5 gm.
	Bentonite solution (2½ per cent) . . . . .	120 cc.
M. Sig.:	Apply to face at night.	

The use of this lotion should be discontinued at the first sign of irritation. The use of a small amount of the lotion at the start of treatment and gradually increasing it at each application will usually prevent this trouble.

In mild cases of shiny noses accompanied by only a few papulo-pustules, it is often sufficient to prescribe a talc containing 2 per cent of *colloidal sulfur*. This is dusted on the face twice daily.

*Blackheads* may be removed by applying a liberal coat of cold cream containing 3 per cent of *resorcinol*. After an hour or so a towel wrung out of steaming water is laid on the face. Or the patient may place his head over a widemouthed kettle of steaming water to which  $\frac{1}{2}$  teaspoonful of spirits of camphor has been added. Expression of the blackheads with a

little implement of the kind obtainable at any drug store is then relatively simple.

*Roentgen therapy* has proved of great benefit in acne. It is the method of choice in the management of the severer types. Before beginning treatment with roentgen rays, the physician should explain to his patient that such treatment does not cause scars. The lesions of acne themselves cause the scar, especially if they are squeezed. Discussion of this point with the patient before treatment is of great importance, for in this way the physician will avoid a great deal of explanation and embarrassment at the conclusion of treatment. A discussion of the technic, indications and contraindications for the employment of roentgen rays in acne is beyond the scope of this clinic. An experience of sixteen years in this field has convinced me that roentgen rays are our best weapon in fighting the ravages of acne.

The *care of the scalp* is essential to the successful management of acne. This applies equally well to seborrheic dermatitis of the face. Most of these patients are beset with dandruff, usually accompanied by itching.

Frequent shampoos with ordinary soap or tincture of green soap are indicated. A few drops of the following lotion, well rubbed into the scalp several times a week, suffice to allay the itching and scaling:

R. Resorcinol monoacetate . . . . .	5.0 gm.
Salicylic acid . . . . .	1.5 gm.
Castor oil . . . . .	3.0 gm.
Alcohol (70 per cent) sufficient to make . . . . .	120 cc.
M. Sig.: Apply to scalp.	

#### MYCOTIC DERMATITIS (RINGWORM)

The feet and hands are most commonly infected with fungi. Secondary involvement of the groin and perianal region is next in frequency. The type of fungus or yeast in any particular case is of little importance from a therapeutic standpoint.

An understanding of the principles underlying the treatment is essential to the successful management of a case of ringworm infection. Fungi grow best in an alkaline medium, therefore it is advisable to dust the feet and the skin between the toes daily with an acidulated powder such as borated talc. Moisture also furthers the growth of fungi, consequently care must be exercised in keeping the skin between the toes dry and free from sweat. The reaction of this sweat is slightly alkaline, producing an optimal medium for the growth of fungi.

The patient who consults his physician for relief of swollen feet with a few streaks of red showing on the leg should be hospitalized. Immobilization of the extremities and hot, wet dressings are indicated. When the acute stage is over, with its inherent danger of phlebitis, recourse may be made to soaking the feet in weak solutions of *potassium permanganate*. This should be done daily until all blisters have disappeared and new skin has formed. It is advisable to continue the foot baths at weekly intervals thereafter in order to reduce the hyperhidrosis and bromidrosis that are often present in these cases.

Should the skin between the toes remain macerated and fissured, the patient is told to paint these areas twice a week with a fungicidal solution. Because of its great fungistatic power, I favor the use of the aniline dye known commercially as *brilliant green*. This is dissolved in equal parts of benzol and alcohol. Vigorous rubbings with an ointment containing from 3 to 5 per cent of *crude coal tar* are efficacious in eradicating the dry, hyperkeratotic and scaling lesions of ringworm.

Persistence in the treatment is essential. Many months are required in curing mycotic disease.

*Tinea versicolor* usually responds to swabbing the affected areas several times daily with a 10 per cent aqueous solution of sodium thiosulfate.

### IMPETIGO

In the newborn this disease, formerly called "pemphigus neonatorum," has greatly decreased in frequency since the practice of washing baby with soap or oils has been largely discontinued. Impetigo neonatorum must be differentiated from pustular folliculitis of infants.

Impetigo of the newborn is highly infectious and cases of this disease should be isolated. Mild antiseptic baths containing *boric acid* are of value. Bullae should be opened and areas painted with an antiseptic preparation. Dusting the skin with a calomel powder is advisable.

Impetigo in the adult usually responds favorably to an erythema dose of *ultraviolet* radiation. A water-cooled apparatus produces copious desquamation, and besides is bactericidal in its action. The timeworn use of ammoniated mercury ointment in this disease has fallen into disfavor, since experiments show that pyogenic organisms such as the staphylococcus and streptococcus can grow in its very midst.

Persons with impetigo are told to rub in vigorously several times during the day a dusting powder containing 6 per cent

each of calomel and boric acid. Avoidance of washing with soap and water is essential.

### WARTS

The small, flat wart that is encountered so often on the *face* and *neck* can be safely removed with a light touch of the electrocautery. The pain is considerably less than with the electrodesiccating needle. No scar will result, because warts are acanthomas, *i.e.*, benign hypertrophic tumors of the epidermis without involvement of the cutis. Pedunculated warts and soft fibromas are easily eradicated in this manner.

Warts on the *eyelids* should be removed, otherwise there is danger of the virus falling into the eye and causing infection of the cornea.

Verrucae on the *hands* can usually be scraped off with a small curet. Bleeding is controlled by pressure. The electrocoagulating electrode may first be applied to the wart.

Painful *plantar* warts offer a somewhat difficult therapeutic problem. Two skin units of x-rays, about 700 roentgens, administered to the wart with careful screening of the surrounding skin often suffice to stop the pain. The wart may persist, but it causes no further discomfort to the patient. The application of radium is equally efficacious. Caution must be exercised in not overtreating warts with x-ray and radium, for ulcers produced in this manner are painful and are difficult to cure.

A drop or two of *bichloroacetic acid* to a wart often works miracles. This acid has an affinity for keratin tissue. Warts, nevi and small tumors will vanish without leaving a trace with the judicious use of this acid.

### HERPES SIMPLEX AND ZOSTER

For many years I have practiced *vaccination* of patients afflicted with simple herpes. A vesicle is opened and its contents scarified into a previously selected area of skin. Local reactions occur in about 30 per cent of patients treated in this manner, and it is just these individuals who remain free from further attacks. Lately the use of smallpox vaccine has produced better results.

The pain of herpes zoster often responds favorably to *iodine* medication. Intravenous injections of sodium iodide in conjunction with large doses of potassium iodide by mouth seem to ameliorate the suffering. Heat may be applied locally, followed by dusting with a borated talcum powder.

## URTICARIA

The cause of a given case of urticaria is frequently not apparent. The physician may eliminate such factors as insects, emotion, disturbances of the liver and gastro-intestinal tract, marital incompatibility, foods, drugs and cold allergy, and still the hives persist. The danger of overlooking drugs such as *quinine* and *aspirin* as etiologic agents in producing urticaria is great. Patients do not regard aspirin as a drug. Sometimes they wilfully conceal the fact that they are taking medicines. But the largest source of error lies in the enormous number of commercial preparations that contain these drugs without the patient or physician being aware of their presence.

In a severe attack of hives accompanied by difficult breathing, the subcutaneous injection of 0.5 cc. of a 1:1000 solution of *adrenalin hydrochloride* is advisable. This may be repeated within one hour. After this has been done, from 5 to 10 cc. of blood are withdrawn from the arm and immediately injected into the buttock. This procedure has given me a higher percentage of cures than any other method.

The shibboleth of the *scratch test* in urticaria has brought many a patient to the point of starvation. The pathogenesis of this disease is intimately connected with the vascular system and not primarily with the epidermis, so that deductions made from positive reactions in this test are obviously inadmissible. I allow patients with hives to eat anything they desire, unless it is self-evident that strawberries or shell-fish are causing attacks. The administration of calcium has proved a failure. A few teaspoonfuls a day of a simple syrup of bromides do excellent service in calming the patient.

Most persons with hives feel comfortable lying in a tubful of warm water. Some boiled oatmeal contained in a cheese-cloth bag may be pressed into the water. After a prolonged bath in this oatmeal water, the skin is patted almost dry and liberal amounts of borated talc are applied. Avoidance of excessively warm, rough clothes and bedding is imperative.

## PITYRIASIS ROSEA

Repeated assurances that the disease is not contagious and that it will not leave scars are the essential points in the management of pityriasis rosea. A few exposures to ultraviolet radiation help to shorten the course of the disease. On the other hand, it is equally true that desquamation caused by the lamp produces itching that is often worse than the disease



itself. And so it was with the treatment prescribed by my grandfather—the application of a strong sulfur ointment.

### PSORIASIS

A *change of climate* often produces a decided improvement in psoriasis, especially in those cases complicated by arthritis.

No specific remedy against this disease exists. Nevertheless, as physicians, we must warn patients against the danger of neglecting treatment. Untreated psoriasis has a tendency to spread over the entire body. People with psoriasis should get as much sunshine as possible, wear light, white clothes, and apply an ointment to the lesions at least every other night. Those who are eating too much fat should reduce its intake. A little *desiccated thyroid extract* taken daily occasionally works wonders. In other patients a course of *Asiatic pills* brings an involution of the lesions.

*Whole blood injections* have proved of value in preventing a fresh spread of the disease, especially if the attack occurs in the summer or winter.

The choice of a topical medicament is difficult. Depending on the amount of cutaneous involvement, varying strengths of *ammoniated mercury* ointment may be used. For large areas it is best to begin with a 3 per cent ointment containing 2 per cent of salicylic acid with which to remove the scales. A patient who has never rubbed mercury on his skin should first be tested for possible idiosyncrasy to this drug. Some patients do better with an ointment of *crude coal tar*, especially if they own a sun lamp which they can use in conjunction with the ointment.

The efficacy of *roentgen rays* in psoriasis is great, especially at first, but the inherent danger of overtreatment through a period of years overshadows its benefits. Psoriasis often appears at points of pressure, as where the strap of a golf bag rubs on the shoulder.

### SCABIES

The diagnosis of scabies is often not made because the physician simply does not look for the typical lesions in the areas of predilection. In children the totally different aspect and localization of scabetic lesions from those in adults render the diagnosis difficult.

*Sulfur* has proved the most efficient and economical remedy in the treatment of scabies. Every druggist has the official sulfur ointment on his shelves. This contains 15 per cent of

sulfur. By mixing this ointment with varying proportions of vaselin, the desired strength is readily obtainable. Children usually tolerate 5 per cent sulfur well.

The full strength ointment may safely be prescribed for dark-haired men. A 10 per cent ointment is well tolerated in the majority of adults and suffices to eradicate the itch mite.

The technic of applying the ointment is important. Before its first application, the patient is instructed to take a hot bath, scrubbing his skin well with soap. The underclothing and bed linen used by the patient should not be changed until the course of treatment is completed. No baths are taken in the interim. The ointment is reapplied each night for two nights. On the morning of the fourth day a bath is taken, all the clothes sterilized by boiling and no further treatment is employed unless dermatitis appears.

### ROSACEA

Rosacea may be associated with acne, but its mechanism of production is entirely different. The disease occurs chiefly in women over thirty years of age. A characteristic feature of these cases is weakness of the abdominal musculature and ptosis of the internal organs. A fluoroscopic examination reveals a delayed emptying time of the stomach. A low gastric acidity is often found. The muscular hypotonia is extended to include the smooth muscle fibers of the blood vessels of the face. Poor muscular tone of this character cannot withstand the strain of constant dilatation and finally gives up the fight altogether. The vessels remain dilated and the clinical picture of flushing, dilated blood vessels and purplish discoloration is complete.

Measures should be adopted to prevent this cycle of events. Hydrotherapy, correct posture and massage are important adjuncts of therapy. Avoidance of alcohol and hot and spicy foods is manifestly necessary. To aid digestion the following prescription has proved of value:

R Hydrochloric acid .....	10.0 gm.
Pepsin scales .....	10.0 gm.
Compound elixir of pepsin sufficient to make .....	170 cc.
M. Sig.: Take 5j in a little water after meals, through a glass tube.	

The irritating action of soap should be avoided. An ointment containing from 2 to 4 per cent of *ichthylol* and 4 per cent

of *sulfur* incorporated in a greaseless base has proved beneficial. This is applied at night.

The action of *x-rays* in this disease is unpredictable. Many cases respond favorably to a few small treatments, whereas others grow alarmingly worse. Good results in rosacea can be obtained only by judicious use of all the methods of treatment. For example, if the *x-rays* have aggravated the condition, it is best to stop all topical medication other than frequent applications of cold solution of aluminum acetate.

## CLINIC OF DR. WALTER H. NADLER

### PASSAVANT MEMORIAL HOSPITAL

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#### TREATMENT OF THE COMMON COLD

THE common cold is the most frequent of all infections and is responsible for an almost incalculable loss of time and work. A compilation of papers on the subject, published in 1932, made up a volume almost as bulky as the present Chicago Telephone Directory. However, but little progress has been made as regards treatment. Active management remains largely symptomatic, and avoidance of contact with persons who have colds is still the best means of prevention. Before attempting to evaluate therapeutic measures it seems necessary to describe briefly the so-called common cold, to consider present views as to its cause, and to review certain physiologic functions of the nose.

#### TYPES OF COLDS AND THEIR ETIOLOGY

The "common cold" evidently is not a disease entity. The *epidemic form*, highly contagious and self-limited, is believed to be due to a filterable virus. Transmission experiments have been successful in the chimpanzee and in humans. The antigenic properties of the virus are weak and the immunity produced is of short duration. The virus infection, itself, lasts only three to four days. Subsequent symptoms are apparently caused by secondary bacterial invasion, and complications are certainly due to these organisms. *Sporadic colds* are evidently of varied origin. Many are undoubtedly caused by the cold-virus, but no practicable method of etiologic diagnosis is available. Other colds, it seems certain, are due to primary infection by one or more of the bacteria found in the nose and throat, such as *pneumococci*, *streptococci*, *staphylococci*, *Micrococcus catarrhalis*, and the *influenza bacillus*, the same organisms responsible for secondary invasion in virus colds.

Factors that lower general resistance to infection or that disturb the function of the nose undoubtedly play a part. Ac-

cordingly, *debility, chronic disease, dietary deficiency, fatigue* and *exposure* are predisposing factors because they lower general resistance. Hot, dry or dust-filled air, freezing temperatures, and sudden changes from one extreme of temperature to another, as well as smoke and other irritating fumes, cause overwork of the nasal mucosa. Chilling of a distant part of the body may produce a reflex congestion of the nose. Local pathology, as *chronic sinusitis, polypi, adenoids* and *chronic tonsillitis*, may cause mouth-breathing and favor bacterial infection. Allergic rhinitis and drug reactions, as from iodides, not only simulate colds but may predispose to infection.

Use of the term "common cold" to include different types of infection seems unfortunate even though the various kinds are often indistinguishable clinically. It might be less confusing to describe the syndrome as an "acute upper respiratory infection" and to distinguish, if possible, between various causes. The term "common cold" could then be applied exclusively to the virus cold.

The *nose* is an active organ whose functions include warming and moistening air of varying temperatures and humidity before it reaches the lungs. It has been estimated that as much as a pint of water is transferred daily from the nasal cavities to the lower respiratory tract. Some impurities are removed by the fine hairs just inside the nostrils and by the mucous secretion of the lining membrane. The nasal mucosa is covered by a layer of ciliated, columnar epithelial cells and scattered "goblet" cells and is continuous with that of the accessory sinuses. The functional efficiency of the nasal membrane depends largely on automatic vascular control. The tissue is very vascular and contains a plexus of veins whose channels anastomose freely. Cavernous blood spaces having the appearance of erectile tissue are present, most numerous along the free border of the inferior turbinate and on the posterior ends of the middle and inferior turbinates. Cycles of congestion and retraction occur normally. Overwork may obviously be caused by sudden changes in temperature and by exposure to dry, hot, cold or dust-filled air. The vascular channels dilate, the mucosa swells, and the nasal passages are narrowed as a result of infection, local irritation, drugs such as iodides, and anaphylactoid states. Constriction is caused by cold air and by certain drugs. Heat or cold applied to the skin of remote parts of the body causes reflex changes in the vascularity of the mucosa. Diet and endocrine dysfunction may exert an effect.

The *symptoms* of a cold are familiar to everyone. The inflammation may be confined to the nose or start in the nasopharynx or pharynx; it may quickly extend to the sinuses or larynx. The typical cold begins with dryness and prickling of the nasal passages, nasopharynx and pharynx. Chilliness and feverishness with but little, or sometimes no, rise in temperature, are due to constriction of the peripheral vascular system. Profuse watery nasal discharge and, usually, sneezing follow. After a day or two the discharge becomes thicker and the nasal passages are obstructed. If secondary invasion does not follow, recovery may occur in three or four days. With secondary invasion the discharge becomes mucopurulent or purulent, the nasal passages are completely blocked, and there is marked increase of the bacterial flora, usually of one organism. Constitutional symptoms, such as malaise, head and muscle aching, and feverishness, become more marked. Symptoms gradually recede and recovery is usually complete in ten days. Persistence and reappearance of symptoms are due to complications of which sinus infection is the most common. Laryngitis and bronchitis are frequent, otitis media and mastoid infection are more serious, and pneumonia is the most dangerous complication.

To recapitulate, the so-called common cold varies in etiology and communicability, in the combination and severity of symptoms, and in duration. The nasal mucous membrane reacts in practically the same manner to inflammations caused by ultramicroscopic viruses, by bacteria, or by both kinds of agents in the same individual. It is not remarkable then, that mild cases of *influenza* can not be distinguished from an ordinary cold, for influenza is caused by a filterable virus somewhat similar to the cold virus but transmissible to ferrets and mice. Nor is it surprising that *allergic manifestations* may be interpreted as colds. Adding to the difficulty of diagnosis is the well known fact that *acute contagious diseases in children*, such as measles, whooping-cough and anterior poliomyelitis, present at the start the picture of an ordinary cold.

#### TREATMENT

There is no *specific* treatment for colds. Serum for the production of passive immunization is not available, even for virus colds.

**Sulfanilamide.**—It is possible that chemotherapy may, in the future, provide a means of attack. Sulfanilamide has been used, as might be expected. The claim has been made

that although the drug has no action in the virus stage, both secondarily infected virus colds and colds due to primary bacterial infection are cut short by its use. That sulfanilamide is of benefit in ordinary colds is impossible to prove. There is no justification whatsoever for its use in early treatment. The great majority of colds are mild and there is no practicable means of determining the type of infection that is present, nor of predicting its duration. To be effective, fairly heavy dosage is required and, to be safe, careful observation of the blood and urine is necessary. According to our present belief, large amounts of sulfanilamide are needed to produce bacteriostasis. For example, 0.1 gm. per kg. of body weight per day (1 gm. per 20 pounds daily) must be given for two or three days in order to produce a blood concentration of 6 to 8 mg. per cent, which is believed to be optimal. It appears that some physicians use three or four tablets of sulfanilamide daily (15 to 20 grains, or 1 to 1.3 gm.) in the treatment of colds.

According to our present knowledge *such treatment is worthless*. In selected cases, however, if after the fourth or fifth day, constitutional symptoms are severe and there is reason to suspect a *streptococcal* infection, and particularly if cultures from the nose and throat show hemolytic streptococci, the use of sulfanilamide in full dosage may be justifiable. Should *otitis media* develop as a complication, sulfanilamide is obviously indicated. Prompt use of this drug will usually forestall mastoid infection. The development of pneumonia is the signal for treatment with a specific type of pneumococcus serum, a preparation of the sulfanilamide group, or both.

**Drugs.**—Trial and error methods of treatment have been legion and still persist. Many drugs have been tried and most of them discarded. The administration of *atropine* in the early stage of a cold seems distinctly unphysiological. Alkalinization has been advocated on the grounds that, sometimes, particularly in children, slight acidosis is present, but the use of *alkalies* has not proved of general value. Chlorine treatment and infra-red heat have been used. Local applications, irrigations and tampons are sometimes employed but they have no physiologic basis. There is no rational indication for the use of antiseptics, such as organic *silver preparations*, since it is not possible to bring them in direct contact with all of the organisms in the nose. The fact is the nasal mucosa is responsible for its own defense. Proof of the value of many of the procedures proposed is almost impossible to establish because colds are self-limited.

**Symptomatic Treatment.**—Symptomatic treatment is of value. Certain measures are rational, relieve symptoms and favor restoration of the function of the nasal mucosa. They may hasten recovery and prevent complications. There is no proof that a cold can be “aborted” except in this sense.

At the onset all colds should be considered *contagious* even though some forms are not readily communicable, and an effort should be made to protect others from contact with the patient or at least, with secretions from his nose and throat. The most important therapeutic measure—rest—facilitates isolation of the patient or prevention of contact with others. Protection of those who are necessarily exposed may be provided by observing “infectious precautions,” including the use of masks.

Our aim for the patient is to keep him comfortable and to establish conditions that favor early recovery from a self-limited infection. Early *bed rest* offers the best means of attaining this object. If colds are apt to be severe or if complications might be dangerous, as in children, the aged, or in the presence of chronic disease, bed rest must be insisted upon. In practice, bed rest is too often neglected because the patient, unmindful of the frequency of secondary infection and of possible dangerous complications, wishes to or feels that he must continue his usual activity. Rest in bed should be continued as long as constitutional symptoms are present and resumed if they reappear. In any event, rest at home is desirable for the first two or three days during the period of contagiousness. A warm room with adequate moisture in the air favors restoration of function of the nasal membrane. Smoking, if not voluntarily forsworn, should be forbidden.

At the *onset* of a cold, agents that produce vasodilation will relieve feverishness and lessen nasal turgescence. External *heat*—a warm bath or even a hot foot-bath—is of value if the patient goes to bed immediately. A glass or two of hot lemonade may produce desirable mild sweating. *Fluids* in the form of fruit juices should be pushed to tolerance. The *diet* should be light but otherwise unrestricted. *Cathartics* are unnecessary unless constipation is present, in which case a mild saline such as dibasic sodium phosphate, a teaspoonful in hot water before breakfast, is advisable. An enema of a pint of warm water may be used instead. A satisfactory *diaphoretic effect* is obtained by the use of whiskey or of salicylic acid preparations. Spiritus frumenti, 1 or 2 ounces, diluted and given as a hot drink at bedtime, is effective. *Acetylsalicylic*



*acid*, or sodium salicylate, grains 10 (0.6 gm.) at four-hour intervals during the day, is useful and should be continued for forty-eight hours or longer if symptoms persist. *Sodium bicarbonate*, grains 15 ( $\frac{1}{4}$  level teaspoon of baking soda), may be given with these drugs in order to prevent or relieve gastric distress.

Other drugs frequently used and of special value *later in the course* if fever and constitutional symptoms are present, are *acetophenetidin* (phenacetin) grains 5 (0.3 gm.) or a combination of acetophenetidin, grains  $2\frac{1}{2}$ , acetylsalicylic acid, grains  $3\frac{1}{2}$ , and caffeine, grain  $\frac{1}{2}$ , repeated at intervals of six hours. Narcotics such as codeine and morphine are undoubtedly effective but their use is usually unnecessary and unwise. A combination of *codeine* and *papaverine* (codeine sulfate, grain  $\frac{1}{4}$  and papaverine hydrochloride, grain  $\frac{1}{4}$ ), five times a day for three days, has been recommended at the beginning of a cold, but the routine use of these drugs seems inadvisable since equally good results seem to be obtained by other means.

In the stage of *complete nasal obstruction* and mucopurulent or purulent discharge another group of drugs provides great relief. A grateful shrinking of the nasal mucous membrane is produced by *benzedrine*, inhaled two to three times through each nostril at intervals of two to three hours. It is important that directions be followed and overdosage avoided. *Ephedrine hydrochloride* or *sulfate*, 1 per cent aqueous solution, or *neosynephrin*, 0.25 per cent solution, two or three drops in each nostril every three or four hours, are of equal value. In order to insure contact with the entire nasal mucosa instillation is made with the head fully extended; when the drops have reached the back of the nose the head is flexed and lowered. Aqueous solutions, properly buffered to avoid local irritation, are advised instead of an oil medium because of the possibility of intratracheal aspiration of oil.

**Treatment of Cough and of Complications.**—Of special symptoms that may be distressing, *cough* is the most important. Codeine sulfate or phosphate, grain  $\frac{1}{2}$  in the form of triturate tablets or in a syrup at four-hour intervals, is most commonly used. If the secretions are tenacious, ammonium chloride, grains 15 every four hours, is helpful. If the drug produces nausea, enteric coated pills may be used. Iodides are of less value, though syrup of hydriodic acid, dr. 1 (4 cc.), is a good mild expectorant, especially for children. If a gargle is desired, warm salt solution, a level teaspoon of sodium

chloride to a glass of water, is as effective as any. *Hoarseness* due to laryngitis is relieved by inhalations of steam.

With the appearance of complications, the horizon of treatment widens. Most important is the use of sulfanilamide with the appearance of *otitis media* or *streptococcus sore throat*, and the use of one of the preparations of the sulfanilamide group with or without specific pneumococcus serum in *pneumonia*. No more striking therapeutic effects are obtained in the field of medicine. But these complications are beyond the scope of this discussion.

### PREVENTION

The highly contagious virus cold cannot be prevented in a susceptible individual who has been directly exposed. One may, of course, escape infection if he has acquired an immunity as the result of a recent cold; such immunity is of variable, but usually short, duration. Attempts to produce active immunity by subcutaneous injections of living *cold virus* have met with failure. It seems probable that many people have a slight degree of immunity which is lost under conditions which lower their general resistance or that cause functional overwork of the nasal mucosa. Such conditions may explain the very frequent recurrence of colds in some individuals. Individual susceptibility may vary from year to year. Two colds a year, in the spring and fall, are the average; some persons are affected six or seven times and a few have so many colds that they seem almost continuous.

The *principles* of prevention are simple but very difficult to carry out. Direct or indirect contact with secretions from a patient in the early stage of an acute cold is usually followed by symptoms within thirty-six hours. The problem is to *avoid such contact*. Rigid control is possible in small units such as the home, schools and hospitals. Children with colds should, of course, be kept out of school for several days. The custom of kissing children is, fortunately, becoming outmoded, even by candidates for public office. In families, avoidance of contact should not be too difficult. If isolation of the patient for a few days is impossible, he can at least sleep alone, his handkerchiefs can be disinfected, and other members of the family can be protected against coughing and sneezing.

If an individual has only one or two colds a year, probably no attempts at prevention should be made. If colds are much more frequent his case should be sized up as an individual problem. A detailed history, complete physical examination

and routine laboratory procedures are clearly in order. Search should be made for *local pathology* in the nose and throat. If *chronic sinusitis* is present, special treatment is indicated. Removal of *adenoids*, *nasal polypi*, or chronically infected *tonsils* may decrease the frequency of colds. An *allergic* state should be ruled out; the appearance of the nasal mucous membrane is suggestive and smears may show many eosinophils. The habits of the patient should be investigated as regards smoking, dress, exposure, hours of work and sleep, exercise and diet. His state of nutrition and rate of metabolism may have a bearing on the problem. Any deviations from good hygiene should be corrected.

**Diet.**—Diet obviously is important if the patient is markedly over- or undernourished. Of equal importance is the question of a *balanced* diet. Inquiry should be made as to whether the patient regularly includes in his diet foods that insure the presence of adequate protein, vitamins and minerals. If his diet has been manifestly deficient in any of these respects, the necessary corrections should be made. There are few practicable laboratory procedures available to determine whether a diet that is apparently deficient according to accepted standard has, in fact, produced a measurable deficiency. Obviously, a large margin of safety exists and there are various compensatory mechanisms. A blood count will show whether there is any iron deficiency. The blood concentration of ascorbic acid can be determined. Vitamin A and B<sub>1</sub> deficiency can be tested, but the methods are not as yet practicable clinically. If a general or a particular vitamin deficiency is suspected, the use of multiple vitamin or of a specific vitamin preparation is indicated and treatment should be continued long enough to insure that an adequate store has been built up. A balanced diet will then supply sufficient accessory food factors. The routine use of vitamin preparations in healthy adults who follow a normal diet and who have no more than one or two colds a year is certainly unnecessary. During growth, in childhood and in youth, however, accessory vitamins are frequently advisable; in fact, their routine intermittent use may be desirable.

**Metabolic Factors.**—That the state of metabolism may be a factor is in accord with clinical experience. Some individuals who have very frequent colds are benefited by small amounts of *desiccated thyroid gland*, particularly if an allergic factor is present. Some of these patients have a basal rate of minus 16 per cent or lower; in others, reported rates of minus

4 to minus 12 per cent may not represent the true basal rate. One might expect other endocrine disorders to predispose to colds, but no observations of therapeutic importance have been made. It is of interest that the topical use of *estrogenic substances*, such as amniotin-in-oil in the form of a nasal spray, has been reported of benefit in the treatment of atrophic rhinitis, but this has no direct bearing on our subject.

**Vaccines.**—Vaccines remain to be considered. Since a filterable virus has come to be accepted as a cause, all claims that bacterial vaccines will prevent this type of cold have been abandoned. The question now is whether bacterial vaccines will prevent or cut short secondary invasion of virus colds or do the same to colds caused primarily by bacteria. Impressions are, on the whole, favorable, but statistical proof is lacking. For, as has been stated, the number and severity of colds vary spontaneously in an individual from year to year. An autogenous vaccine might be expected to be the most effective if cultures were made at the proper time and if the vaccines were properly prepared. Mixed, stock vaccines, however, seem often to be of benefit both on subcutaneous and on oral administration. Whatever immunity may follow is apparently specific in some instances and nonspecific or related to responses to heterophile antigens in others.

If *mixed, stock vaccines* are used, frequent small injections over a rather long period of time seem preferable. The best method of administration seems to be weekly, subcutaneous injections, starting with 0.1 cc. and increasing the dose 0.1 cc. every week, if no reactions occur, to a maximum of 1.0 cc. The largest dose reached may then be repeated at intervals of two or three weeks over a period of months, in an attempt to maintain immunity. This method may be inconvenient and expense may be an objection.

*Oral cold vaccines* can be administered by the patient, himself, and seem to be equally effective. The oral vaccines contain killed bacteria of high heterophile antigen content and include such organisms as pneumococci, streptococci, Hemophilus influenzae, and Micrococcus catarrhalis. The patient is instructed to ingest the vaccine in the fasting state and postpone breakfast for one hour. The dose is repeated for seven days and, thereafter, once or twice a week. It is best to start very early in the spring and continue until summer, and it is equally important to start early in the fall before colds are prevalent and to continue during the winter.

It should be mentioned that the use of all mixed cold vac-

cines has been condemned by some writers, not because of any danger but because of alleged uselessness. Actual statistical proof of their value is, of course, almost impossible to obtain. The general clinical impression, nevertheless, is that they may be effective. In the present state of our knowledge, their use is justifiable provided that one realizes that their action is not certain and makes this point clear to the patient, and provided that general and local factors that predispose to colds have not been overlooked.

PUBLIC HEALTH ASPECTS.—Treatment has been considered almost entirely from the standpoint of the individual even though colds constitute a public health problem of great importance. Whether wholesale *vaccination* of large groups of people in schools, industries and camps would reduce the total number of colds and would make the individual infection milder and less likely to be followed by a dangerous complication is not certain. The interpretation of favorable reports has been criticized on various grounds. Some writers insist that no conclusions are justified unless control groups were given placebos, such as the injection of sterile water instead of vaccine or the use of capsules containing lactose instead of oral cold vaccine. In some instances, as might be expected, patients who received only placebos believed that they were benefited. Other writers call attention to the unreliability of the testimony of many individuals as to the number and severity of colds contracted over a period of a year. It seems evident that trials have not been made on a sufficiently large scale under controlled conditions to warrant a definite conclusion.

Pending the discovery of a sure means of vaccination against colds, education of the general public should be continued. If the knowledge is widespread that colds are communicable and potentially dangerous, attempts will more frequently be made to avoid exposure, to shorten the course by appropriate treatment, and to safeguard others.

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SEROTHERAPY AND CHEMOTHERAPY OF  
PNEUMOCOCCUS PNEUMONIA

THE progress which has been made in the therapy of pneumococcus pneumonia is characteristically illustrated by the studies reported from the Cook County Hospital. Chronologically these observations begin with the report<sup>1</sup> of a study of a control group of patients treated by symptomatic measures employed prior to the advent of antipneumococcic horse serum. This was followed by a publication detailing the experience with the use of concentrated and refined rabbit serum.<sup>1</sup> Further communications have dealt with the employment of sulfapyridine in a large group of cases.<sup>2, 3, 4</sup> The most recent publication describes the results with sulfathiazole.<sup>6</sup> The combination therapy of the newer drugs with immune serum constitutes one phase of the many investigations.

THE CONTROL STUDIES

Mortality statistics have demonstrated averages ranging from 35 to 40 per cent. The investigations, however, were totally inadequate for types of pneumococci encountered until the publication of a control series of 164 patients. Obviously clinical case controls can no longer be employed because observation of Table 1 demonstrates a mortality percentage of 38.4 while the results of modern therapy show results well below a 10 per cent mortality. No investigator is justified in adopting a control series employing only symptomatic therapy.

Table 1 illustrates the effect of *bacteremia* on mortality, which in this series attained 60 per cent. It further illustrates the importance of *type* influence. Thus Type I accounted for

TABLE 1  
CONTROL CASES

Type.	No. of cases.	Deaths.		Bacteremia.			Type.	No. of cases.	Deaths.		Bacteremia.		
		No.	%	No.	Dead.	%			No.	%	No.	Dead.	%
I	49	13	26	10	4	40	XIII	2	0	0	1	0	0
II	34	16	47	6	4	67	XIV	2	0	0	0	0	0
III	18	11	61	1	1	100	XVI	1	0	0	0	0	0
IV	3	2	67	0	0	0	XVII	2	0	0	0	0	0
V	6	5	83	4	3	75	XVIII	2	2	100	0	0	0
VI	2	0	0	0	0	0	XIX	5	2	40	1	1	100
VII	17	6	35	4	4	100	XXI	1	0	0	0	0	0
VIII	8	1	12	2	1	50	XXIII	1	1	100	0	0	0
IX	3	1	33	0	0	0	XXVIII	1	1	100	0	0	0
X	1	0	0	0	0	0	XXIX	1	0	0	0	0	0
XII	5	2	40	1	0	0							
Totals								164	63	38.4	30	18	60

thirteen deaths, or 26 per cent in the nonbacteremic group, while four patients died of the ten with bacteremia, a 40 per cent mortality. Type II showed a mortality of 47 per cent, rising to 67 per cent in those with positive blood culture. The study of this table shows the mortality percentage for the various types. In this series, the effect of age on the mortality is demonstrated by a death rate of 45.7 per cent in the forty-one to fifty year age group, a 56.6 per cent mortality in the fifty-one to sixty age group, 55.5 per cent in the sixty-one to seventy year age period, and 84 per cent died in those over 70 years of age. The death rate of patients over forty years of age in this control group was 54 per cent.

#### IMMUNE SERUM THERAPY

With the introduction of immune serotherapy, the mortality figures showed a pronounced decline.<sup>1</sup> The use of the refined and concentrated *rabbit serum* demonstrated the remarkable efficacy of this therapeutic agent—only one-fourth of deaths when contrasted with the control group. Less than 10 per cent mortality was recorded, whereas the bacteremic death rate dropped to 26 per cent. Table 2, summarizing these studies, illustrates the effect on the individual types. Type I mortality dropped to 6 per cent in the nonbacteremic group, with 16.7 per cent in the positive blood culture group. For Type II, the figures were 8.8 per cent and 50 per cent, respectively.

Rabbit serum has many advantages, both in manufacture and practical use, over the antipneumococcus horse serum. It

TABLE 2

TREATMENT WITH CONCENTRATED AND REFINED RABBIT SERUM: TYPES OF SERUM-TREATED CASES

Type.	No. of cases.	Deaths.		Bacteremia.			Type.	No. of cases.	Deaths.		Bacteremia.		
		No.	%	No.	Dead.	%			No.	%	No.	Dead.	%
I	30	2	6	6	1	16.7	XV	1	0	0	0	0	0
II	34	3	8.8	6	3	50	XVII	1	0	0	0	0	0
III	14	3	21	0	0	0	XVIII	3	0	0	1	0	0
IV	11	1	9	2	0	0	XIX	1	0	0	0	0	0
V	2	0	0	1	0	0	XX	1	0	0	0	0	0
VI	1	0	0	0	0	0	XXIII	1	0	0	1	0	0
VII	26	2	7.6	3	1	33	XXIV	1	0	0	1	0	0
VIII	16	3	18	0	0	0	XXV	2	0	0	0	0	0
IX	2	0	0	0	0	0	XXVII	1	0	0	0	0	0
X	2	1	50	1	1	100	XXIX	2	0	0	1	0	0
							XXXI	1	0	0	0	0	0
Totals								153	15	9.8	23	6	26

Corrected mortality (4 deaths under eighteen hours): 11 deaths (7.2%).

has practically superseded the use of the latter in the immune serotherapy of pneumonia. Sensitivity to rabbit serum proteins is infrequent. While the three tests for sensitiveness are employed, the greatest reliance is to be placed on the *conjunctival test*. The intracutaneous and intravenous injection methods in themselves add very little to the results of the conjunctival testing. They are supplemental and in no way determine the use or contraindication for serum.

**Indications for Rabbit Serum.**—At the present time the following indications for the use of rabbit serum in the type-specific treatment of pneumococcic pneumonia can be predicated. Thus serum is to be used:

1. When the effective sulfanilamide derivatives (*sulfoxydine* and *sulfathiazole*) are contraindicated.
2. When the effective sulfanilamide derivatives produce no measure of improvement in from twenty-four to thirty-six hours.
3. When the appearance of the various toxic effects of the sulfanilamide derivatives develop during administration of these drugs and demand their cessation.

When the following conditions are present, a *combination* of serotherapy and chemotherapy is usually advised:

1. When the history indicates a seventy-two-hour duration of the disease.
2. When the patient is over fifty years of age.
3. When multiple lobes are involved.
4. When blood cultures are positive.
5. In pneumonia during pregnancy or the puerperium.
6. When there is serious concomitant complicating disease.



Serum is usually *contraindicated* in the patient with a positive conjunctival test. However, horse serum and rabbit serum are both available and nonreactor serum can be employed. The aged patient and the very weak individual should be given serum with considerable caution.

It is perfectly obvious from the above discussion that the necessity for sputum typing and blood culture investigation can not be neglected despite the effectiveness of chemotherapy. Recourse to serum therapy is frequently necessary and this decision may be, and often is, sudden. Disaster is invited for the patient by further delay while awaiting for the reports of the type organisms producing this disease.

**Dosage.**—The dosage of serum usually approximates 100,000 units. This is doubled or trebled by such factors as advancing age, bacteremia, increased duration of illness, multiplicity of pulmonary lobe involvement, complicating disease, and severity of symptoms. Types II and III infections demand more serum. Improvement in the symptomatology is the usual guide for efficacy and adequacy of dosage.

When available, reliance is placed on the *Francis test*, the *serum agglutination test*, and the *mouse protection test*. Ordinarily, however, the temperature, pulse and respiration rate with the general condition of the patient determine the indication for more serum. This should be given at four- to twelve-hour intervals, until the desired result is obtained. Retyping and careful, thorough examination of the patient should be carried out when response to adequate dosage of serum is not obtained.

**Method of Administration.**—The method of administration consists of the usual test or trial dose given intravenously followed, after one to two hours, by the remaining calculated dose. The total dosage is frequently given by the *intravenous drip method*, diluting the serum with normal salt solution in the drip flask. With the concentrated unitages now available, the *single total dose method* may be employed, injecting the entire amount undiluted directly into the blood stream. The first cubic centimeter should require two minutes, while the remainder should be injected at the rate of  $\frac{1}{2}$  to 1 minute per cc.

**REACTIONS.**—The serious immediate reactions are best prevented by the careful preliminary testing, although the antidote *epinephrine* should always be ready at hand for immediate use. The onset of a reaction demands immediate cessation of the serum injection. Thermal reactions and the late serum

effects occur frequently. They are disturbing and annoying, but rarely dangerous, and respond promptly to appropriate treatment.

Figure 9 *A* illustrates treatment with concentrated and refined rabbit serum, all the pertinent data being given. Anti-

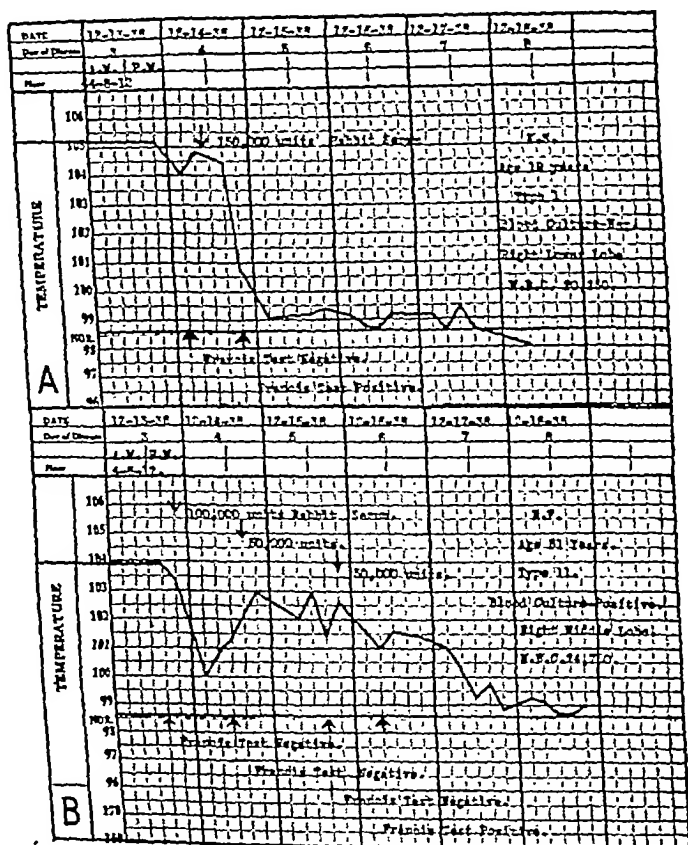


Fig. 9.—Results of treatment of pneumococcus pneumonia with concentrated and refined rabbit serum. See text for details.

pneumococcus serum was given by the single total dose method. The sharp critical form of response is demonstrated in the Type I infection. Figure 9 *B* shows the necessary repetition of serum dosage guided by the Francis test. The injections of serum were continued until a satisfactory clinical

response was obtained and the Francis test was changed from negative to positive.

#### SULFAPYRIDINE THERAPY

The value of sulfapyridine as a therapeutic agent in the treatment of pneumococcic pneumonia was quickly indicated. Early experience with this drug demonstrated an even greater efficiency than immune serum. The first report<sup>2</sup> published from the Cook County Hospital on a series of 160 patients, fifteen of whom had positive blood cultures, revealed a mortality of 3.3 per cent. A later study<sup>4</sup> of 200 patients treated with sulfapyridine showed a 4 per cent mortality—3 per cent in the nonbacteremic series and 7.8 per cent in thirty-eight patients with positive blood cultures.

It is remarkable that in this group of 200 patients, there were forty-seven with Type I infection, none of whom died from the pneumonia. This included eight patients with *bacteremia*. In a report soon to appear describing the use of sulfathiazole<sup>5</sup> (control series treated with sulfapyridine) there were thirty-one patients with Type I infection, three with positive blood cultures; there were no deaths. There is thus demonstrated a remarkable specificity of sulfapyridine in Type I pneumococcus infection. The total group, comprising over 400 patients treated with sulfapyridine, shows results superior to those obtained by serum alone.

**Dosage.**—The dosage has been standardized so that, initially, 4 gm., or eight tablets, are administered followed by 1 gm. every four hours until a normal temperature has been sustained for forty-eight hours. Experience has indicated that associated drug medication or using the powdered drug in various liquids has not materially changed the unpleasant effects. The nausea and vomiting so commonly encountered in the administration of this drug do not seem to be any more frequent or severe by the initial 4-gm. dosage than with the usually advised 2-gm., four-hour schedule for two doses.

In those cases where the initial vomiting was severe and persistent, or in patients unable to swallow the drug, an intravenous injection of 100 cc. of 5 per cent aqueous solution of *sodium sulfapyridine* was administered. This was then followed by the oral dosage after four hours, using 1-gm. doses.

**BLOOD CONCENTRATION.**—Optimum concentration levels in the blood are rapidly attained by the use of the large initial dosage. Blood levels fluctuate moderately on the usual maintenance dose. The clinical response, however, cannot be very

definitely correlated with the blood concentration. While adequate blood levels are difficult to fix, five milligrams per cent of the free sulfapyridine is usually considered as the accepted concentration.

UNTOWARD REACTIONS.—The seriousness of the toxic reactions demands continuous supervision of the patient. Adequate laboratory investigation must be made prior to the onset of therapy. Toxic reactions demand *cessation* of sulfapyridine administration and, frequently, a change to other forms of therapy. This therefore means that the patient must be investigated just as thoroughly as the pneumonia patient was prior to the discovery of sulfapyridine.

The laboratory examinations before drug therapy include as a minimum, *sputum typing, blood cultures, complete blood counts* and *urine studies*. And these must be frequently repeated in addition to the blood concentration studies.

The damaging effects on the red and white hemopoietic organs and cells are not rarely encountered. Acute *hemolytic anemia* is common. One agranulocytic reaction with fatality was experienced. Another case of *aplastic anemia* with agranulocytosis, with a fatal outcome, resulted from sulfapyridine therapy. Various *kidney complications* are met with, such as calculi, anuria, albuminuria and casts, hematuria, and non-protein nitrogen elevation in the blood. *Drug rashes* and *drug fever* must be kept in mind as they occur rather frequently and introduce a puzzling pattern in the clinical picture. *Hepatic injury* and central and peripheral *nervous system effects* are described, but these have not been met with in over 400 patients treated with sulfapyridine.

The *nausea* and *vomiting* are often troublesome; while unquestionably these are of central origin, the intravenous use of the drug may so improve the patient that vomiting lessens. The intravenous fluids and employment of sedatives may frequently accomplish much in reducing these effects. Persistence of administration may acclimate the patient to the drug so that vomiting, initially present, may disappear, although often the opposite result occurs.

It must be kept in mind that as a general rule the toxic reactions appear from relatively *long* and *continued use* of the drug, especially where large total doses are employed. The beneficial effects of sulfapyridine are produced early in its use. An *evaluation*, therefore, should be made after five days of use of the drug; this usually means after 20 to 25 gm. are consumed, provided of course no serious toxic effects appear.

The evaluation should consider the clinical and laboratory evidence at this time. Continuation of medication is decided by this appraisal. The drug is usually stopped after forty-eight hours of normal temperature, although flexibility rather than rigidity of this rule should be stressed. Evidence is available that organisms may become sulfapyridine-fast by interrupted medication. Nevertheless, few relapses occur from drug cessation after the drug is continued during forty-eight hours of normal temperature. In fact, relapses are infrequent in cases

TABLE 3

A STUDY OF 200 PNEUMOCOCCUS PNEUMONIAS TREATED WITH SULFAPYRIDINE

Total.				Nonbacteremic.			Bacteremic.		
Type.	No. of cases.	Deaths.		No. of cases.	Deaths.		No. of cases.	Deaths.	
		No.	%		No.	%		No.	%
I	47	0	0	39	0	0	8	0	0
II	54	2	3.7	35	0	0	19	2	10.5
III	19	1	5.2	19	1	5.2	0	0	0
IV	4	0	0	3	0	0	1	0	0
V	6	0	0	5	0	0	1	0	0
VII	23	3	13.0	18	2	11.1	5	1	20
VIII	19	2	10.5	17	2	11.7	2	0	0
IX	1	0	0	0	0	0	0	0	0
XII	6	0	0	5	0	0	1	0	0
XIII	2	0	0	2	0	0	0	0	0
XIV	2	0	0	0	0	0	0	0	0
XV	1	0	0	0	0	0	0	0	0
XVI	2	0	0	1	0	0	1	0	0
XVII	2	0	0	0	0	0	0	0	0
XVIII	1	0	0	0	0	0	0	0	0
XIX	1	0	0	0	0	0	0	0	0
XX	2	0	0	0	0	0	0	0	0
XXIII	2	0	0	0	0	0	0	0	0
XXIV	3	0	0	0	0	0	0	0	0
XXVII	1	0	0	0	0	0	0	0	0
XXXI	1	0	0	0	0	0	0	0	0
XXXI	1	0	0	0	0	0	0	0	0
Total	200	8	4	162	5	3	38	3	7.8

in which the drug is suddenly stopped when a normal temperature is obtained.

INDICATIONS AND CONTRAINDICATIONS.—In addition to the foregoing toxic reactions, impaired kidney function and hepatic disease should contraindicate sulfapyridine. Curiously, granulocytopenia, the result of bacterial infection, frequently shows tremendous improvement with sulfapyridine. Serious anemias, such as pernicious anemia, sickle cell anemia complicated by pneumonia have responded well as far as the infection is concerned to sulfapyridine medication. Blood transfusions have been frequently employed.

**Methods of Administration.**—Sulfapyridine can be administered by parenteral injection, using the sodium salt.

When given *intravenously*, a 5 per cent solution in distilled water is used, employing from 3.5 to 5 gm. per dose. The injection may be repeated in from twelve to twenty-four hours. If escape into the adjacent tissues occurs, a severe irritating

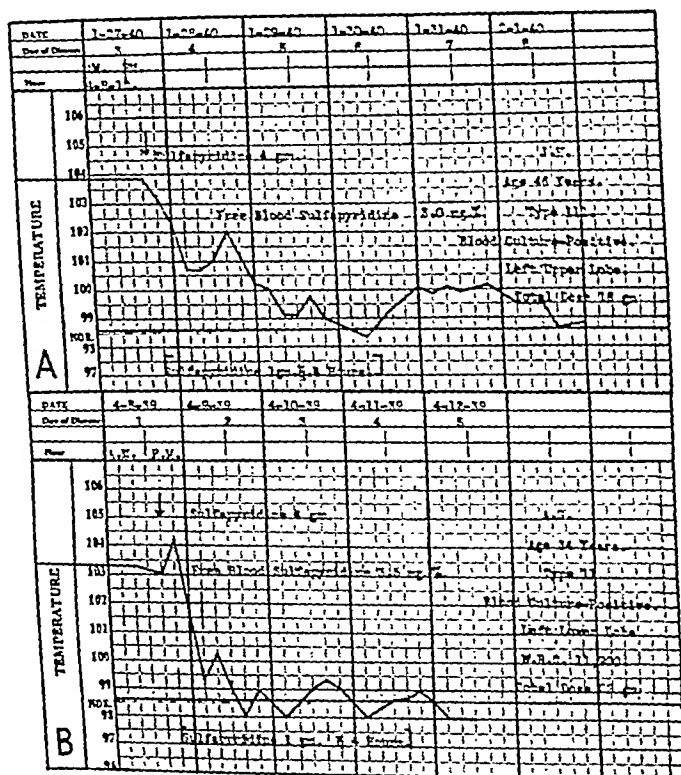


Fig. 10.—Results of treatment of pneumococcus pneumonia with sulfapyridine.

and necrotic effect may be produced. *Subcutaneous* or *intramuscular* injection may also be employed and is frequently very satisfactory; 5 gm. in 1000 cc. of normal salt solution is the concentration advised. No untoward effects have been observed and a steady blood level has been obtained.

**Results of Treatment.**—In the *combined* therapy, using immune serum with sulfapyridine, the results very curiously indicate superiority of sulfapyridine alone over the combina-

tion therapy. This was not the result of selection of cases, *i.e.*, the more seriously ill were not chosen for the combined therapy. Similar findings were reported by the Illinois Pneumonia Control Commission. Further study must determine the adequate explanation of these results.

Table 3 reveals the results obtained by the use of sulfapyridine in 200 cases of pneumococcic pneumonia. Type II pneumonia was responsible for 27 per cent of the cases, with a bacteremic frequency of 35 per cent. Many of the Type II cases had a common origin in a shelter for homeless men who were housed in a school hall. Types VII and VIII showed a higher percentage of Negroes, Type VII being particularly virulent; 58 per cent of these patients were admitted seventy-two hours or more after the onset of the disease. Malnutrition, undernutrition, alcoholism and associated acute and chronic diseases were present in a good number of these individuals admitted to the large charity hospital. Nevertheless, the results indicate the tremendous progress that the therapy of pneumococcus pneumonia has made by the introduction of sulfapyridine.

#### SULFATHIAZOLE

There are unquestioned advantages in the chemotherapeutic management of pneumococcus pneumonia and some evidence to indicate its superiority over immune serotherapy. The *modus operandi* of the recovery induced by drug therapy is not considered as following the immunological pattern created in a serum-induced recovery. Chemotherapy demonstrates effectiveness against nearly all types of infection. The cost is low. The ease of administration is of comfort to both the patient and physician. But efficiency in producing recovery from pneumonia contributes most of all to the popularity of chemotherapy. Theoretically there should be an enhancement of the therapeutic value in the combination of serotherapy and chemotherapy. However, the additive use of these two methods, each of proved value, has not been strikingly more efficient, as comment has already indicated.

In the use of sulfapyridine, definite disadvantages are readily apparent. The nausea and vomiting, so frequently severe, detract from the usefulness of the drug. This effect not only aggravates the illness of the patient, but interferes with the continuation of treatment, whereby entrance of the drug into the blood stream is prevented. The toxicity of the drug is pronounced, as has been pointed out. Many of these results are produced by what is known as *acetylation* or *conju-*

gation of the drug. This readily occurs with sulfapyridine, a major percentage of the drug being conjugated. Acetylated sulfapyridine, chemotherapeutically considered, is inactive and inert. Nevertheless, it is considered responsible for the toxic manifestations and for the renal blocking and calculi formation.

**Advantages over Sulfapyridine.**—Naturally an analogue of sulfapyridine was sought. Many compounds have been tried. The most effective and the least toxic thus far was found to be *sulfathiazole*. The preliminary studies have indicated that sulfathiazole equals sulfapyridine in therapeutic effectiveness when comparative studies were made with various types of pneumococcus infections. On the other hand, *staphylococcic infections* respond more readily to sulfathiazole medication. The drug simulates in its action many of the pharmacologic activities of sulfanilamide rather than sulfapyridine. It is readily absorbed into the blood stream. High levels are quickly attained, and it is excreted into the urine at a rapid rate. The degree of conjugation, both in the blood and urine, is much less than that which is obtained with sulfapyridine. As a consequence, a larger percentage of the total drug absorbed into the blood stream is therapeutically active.

The *toxic effects* are generally not so severe as those induced by sulfapyridine. Thus nausea and vomiting occurred in seven patients in the series of 169 treated, only one requiring discontinuance of the drug. With sulfapyridine, the experience was over 55 per cent, 15 per cent requiring withdrawal of the drug. No evidence of renal irritation was encountered, nor were effects noted on the hemopoietic systems.

**UNTOWARD REACTIONS.**—*Injury to nerve tissue* may appear. *Paresthesia* and *neuritis*, though infrequent, may be severe. *Drug fever*, *drug rashes* and *conjunctival irritation* have been found to be serious manifestations; five instances of this were noted, two of the five ending fatally.

The *mortality rate* in the series of 169 patients treated was 5.3 per cent. In the positive blood culture cases (twenty-four), two died, or 8.3 per cent; in the nonbacteremic series the mortality was 4.8 per cent. The results when compared to a contemporary group of 164 patients treated with sulfapyridine were approximately the same.

**Dosage.**—The method of dosage employed varied from that used with sulfapyridine. An initial 4-gm. dose was followed in four hours by one of 3 gm., subsequently after four hours by 2 gm., and thereafter 1 gm. every four hours. This



method was suggested by the pronounced variation frequently encountered in the blood level, presumably due to the rapid elimination in the urine.

**Results of Treatment.**—Figure 11 and Table 4 show all the pertinent data and illustrate the characteristic forms of temperature response to sulfathiazole. It must be remarked that the sulfathiazole treated patient presents an appearance

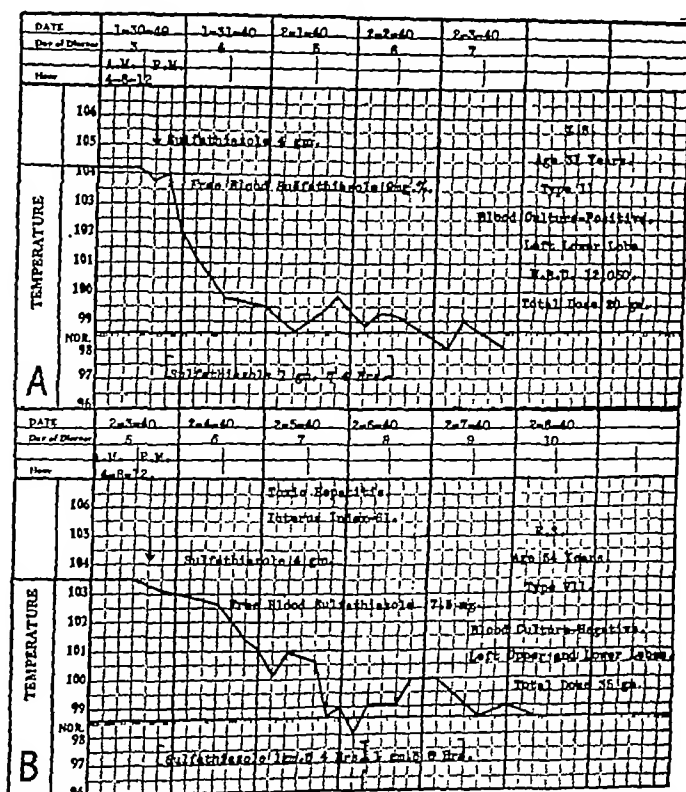


Fig. 11.—Results of treatment of pneumococcus pneumonia with sulfathiazole.

of relative comfort when compared to the nauseated, vomiting individual under sulfapyridine medication. Temperature reduction is produced more rapidly by sulfapyridine therapy. The course of the fever curve shows a declination which is a characteristic combination of crisis and lysis, without the precipitous termination of the former and the absence of the prolonged course of the latter. It resembles a concave trajectory

curve or geometric hyperbola with the normal temperature level attained in the forty-eight to sixty-hour period.

Medication should be continued *at least* forty-eight hours after the temperature reaches normal. Selective effectiveness

TABLE 4  
RESULTS OF TREATMENT WITH SULFATHIAZOLE

Type.	Total.			Nonbacteremic.			Bacteremic.		
	No. of cases.	Deaths.		No. of cases.	Deaths.		No. of cases.	Deaths.	
		No.	%		No.	%		No.	%
I	27	3	11.1	19	2	10.5	8	1	12.2
II	75	3	4.0	62	3	4.8	13	0	0
III	19	3	15.8	18	2	11.1	1	1	100
IV	8	0	0	8	0	0	0	0	0
V	6	0	0	6	0	0	0	0	0
VII	15	0	0	14	0	0	1	0	0
VIII	13	0	0	13	0	0	0	0	0
XIV	1	0	0	0	0	0	0	0	0
XIX	1	0	0	1	0	0	1	0	0
XXI	1	0	0	1	0	0	0	0	0
XXV	2	0	0	2	0	0	0	0	0
XXVII	1	0	0	1	0	0	0	0	0
Total	169	9	5.3	145	7	4.8	24	2	8.3

Per cent with bacteremia: 14.2.

was demonstrated by sulfathiazole. Better results were obtained by sulfathiazole in Type II and VII pneumonia. Sulfapyridine was superior in Types I and III.

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## CLINIC OF DRS. SIDNEY O. LEVINSON AND ALBERT M. WOLF

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### HUMAN SERUM: ITS APPLICATION IN MEDICINE

A CONSIDERATION of the brilliant achievements in the use of antisera of animal origin discloses that they are relatively few in number. It will not be amiss to analyze briefly some of the difficulties encountered in the production of animal sera, and at the same time consider whether these obstacles may be circumvented by the use of the human being himself—rather than animals—as a source for antiserum.

The artificial antigen must be a faithful reproduction, immunologically, of the antigens of the natural disease agent. Otherwise, the resultant antiserum will not be truly specific, nor will it be clinically effective. In many diseases, notably those of virus origin, the failure to produce a potent artificial antigen has balked all efforts to prepare a potent antiserum. This problem is overcome in the use of the convalescent human being as a source of serum; whatever the agent of his illness may be and regardless of the finer immunologic considerations, the patient has received the proper antigen. His serum after recovery might have therapeutic merit. Such natural human antiserum is known as *convalescent human serum*.

If the proper antigen can be produced, the animal selected for immunization has been chosen more on the grounds of convenience and practicability than superiority. Thus the animal of choice in most instances has been the horse. It is not unlikely that man (for whom the disease is natural) would be a better source of antiserum if it were practical to use him for immunization. This has been attempted in a very limited way. A pertussis human antiserum has been prepared by repeatedly inoculating healthy adults. Since the donors had all had pertussis as children, this serum is classed as *hyper-immune*.

In view of the newer knowledge of immunity, it is believed that a foreign serum is not disseminated as rapidly, or utilized as readily, as a homologous serum. This is particularly true in the presence of sensitivity to the foreign serum. Furthermore, homologous serum is devoid of severe reactions and serum sickness, which is a not infrequent accompaniment of foreign (horse) serum. Freedom from sensitization when human serum is used, in contrast to animal serum, is likewise a matter of considerable importance.

In view of the foregoing considerations, the field of human serotherapy is worthy of serious thought. Universal or even extensive success cannot be expected, for there are distinct limitations to humoral immunity upon which serum effectiveness is dependent, whether of animal or human origin. Certain diseases, such as tuberculosis, seem to give rise to no, or at most very little, humoral immunity and are affected neither by human nor animal antisera. Other diseases may be susceptible to treatment but are of such infrequent occurrence as to present great difficulties in obtaining adequate amounts of serum. This difficulty may be overcome in the future by the newer methods of drying serum, the *lyophile* process. Such dried serum is believed to retain its potency for years.

Many difficulties have impeded extended study on the value of human serum (convalescent or immune). The relative inability to secure donors and a resultant sufficient supply of serum for investigation has been a grave obstacle. The limited source of serum has prevented adequate studies to standardize the optimal time for serum collection and optimal dosage for therapy. The meticulous care required in processing human serum has also discouraged efforts at its preparation and study. With all these problems, it is not surprising that only a small part of the possibilities of human convalescent or hyperimmune serum has been explored. Nevertheless, some of the results from limited investigations have been highly gratifying.

Extensive utilization of human convalescent serum is made possible by an organization which will undertake the endless task of finding donors, obtaining their own and physician's consents, drawing blood, processing the serum, and making it available to the medical profession. Such organizations are known as "Serum Centers."

The modus operandi in most serum centers is briefly and essentially as follows:

## THE SERUM CENTER

**DONORS.**—Donors are reported by their physicians, by the State Department of Public Health, the City Department of Public Health, and by other Health officers. After the physician's consent is obtained and the donor is found to be in good health, he is solicited to give blood. Venesection is performed at the Serum Center, the contagious disease hospitals, the patient's home, or at "Serum Clinics" held from time to time at convenient locations. Ordinarily, blood is taken only from adults, in amounts of 250 cc. The procedure may be repeated after a suitable interval and is perfectly safe for the donor.

**PROCESSING OF BLOOD.**—Blood is permitted to clot spontaneously at room temperature and is then placed in the refrigerator for from twelve to twenty-four hours to ensure maximum separation of serum. After centrifuging, the serum is withdrawn, a sample at this time being removed for Kahn and sterility tests. A second centrifuging frees the serum of all the remaining erythrocytes, fragments of clot, etc. Specimens proved sterile and serologically negative are mixed to make a *pool*. The purpose of the pooling is to obtain a uniform product, for an individual serum may be stronger or weaker than the average. Then 0.3 per cent tricresol or 1:10,000 merthiolate is added as a preservative, the serum is passed through a Berkefeld N. filter, and the serum is bottled in ampules of selected capacity. Specimens of the "pool" and bottled serum are again tested for sterility and safety by cultural methods and animal inoculation before the serum is distributed.

Throughout the processing the serum must be kept as cold as possible. Aseptic technic must be maintained throughout the procedure. Careful supervision and accurate records are essential.

**TYPES OF HUMAN SERUM.**—*Convalescent Serum.*—This is an antiserum derived from fully recovered convalescents and obtained during the period of maximum potency.

*Hyperimmune Serum.*—This is antiserum derived from healthy, long recovered individuals who have subsequently been artificially immunized with the antigen; it is obtained during the optimum period following such inoculation.

*Adult Immune Serum.*—This is serum from healthy adults who have had a particular disease in childhood and presumably possess residual antibodies.

*Normal Serum.*—Normal serum is derived from healthy adults for use for intravenous therapy without consideration of its immune characteristics.

## SCARLET FEVER CONVALESCENT SERUM

The modern use of this serum is usually attributed to Riess and Jungmann, although Weisbecker's work in 1897 is of historical interest. The optimum period for taking blood from donors is from the nineteenth day of illness to six months after the date of onset; thereafter the potency of the serum slowly declines. Adult immune serum obtained from donors years after their attacks of the disease still retains some value.

**Scarlet Fever.—Prophylaxis.**—The dose employed here is 10 cc. for *children* up to age ten, and 20 cc. for *adolescents* or *adults*, administered *intramuscularly*.

In a series of 4595 home contacts (Table 1) who gave no history of previous scarlet fever and who were definitely ex-

TABLE 1

SCARLET FEVER PROPHYLAXIS WITH SCARLET FEVER CONVALESCENT SERUM

Age of contacts, years.	No. of contacts.	No. of cases did not contract scarlet fever.	No. of cases developed scarlet fever.	% did not contract scarlet fever.
1-5	1556	1521	35 { 32 Mild 3 Moderate	97.7
5-10	1138	1096	42 { 27 Mild 9 Moderate 6 Severe	96.3
10+	1528	1506	22 { 15 Mild 6 Moderate 1 Severe	98.5
Not recorded	373	366	7 { 1 Mild 5 Moderate 1 Severe	98.1
Total	4595	4489	106 { 75 Mild 23 Moderate 8 Severe	97.7

posed, 97.7 per cent failed to develop scarlet fever after receiving a prophylactic injection of serum. Similar results were obtained in susceptible Dick-positive student nurses inadvertently exposed to the disease by patients.

*Passive immunity* is only temporary. Although from some reports it may last one or two months, only too often it may not persist more than two weeks. For this reason it is advisable to repeat the inoculation at the end of two weeks in a

susceptible individual who remains constantly exposed to the infection for longer than this period.

*Treatment.*—The results secured with the use of serum in the treatment of scarlet fever are now well established. The dose is from 20 to 100 cc., depending on the age of the patient, the severity of the disease and the time of administration. The average dose is 40 cc. The route of choice is *intravenous*.

When administered early and in adequate dosage, the serum produces a prompt amelioration of the acute symptoms of the disease. This is particularly true when it is administered intravenously. Over 90 per cent of patients will have a drop in temperature, decrease in toxicity, fading of the rash and improvement of the throat symptoms within from twelve to twenty-four hours. The rapidity of the improvement depends not only on the time treatment is instituted, but also upon the amount of serum administered and the route employed. Hoyne *et al.* in a study on the value of human convalescent serum stated that 947 hospital patients who were seriously ill at the time of serum treatment had an average drop in temperature at the end of twelve hours of  $1.7^{\circ}$  F., at the end of twenty-four hours of  $2^{\circ}$ , and at the end of forty-eight hours of  $2.6^{\circ}$ . In many instances there were dramatic reductions of 4 and  $5^{\circ}$  within a few hours, but patients suffering from septic complications seldom responded in such an amazing manner.

The study also brought out the very arresting fact that the incidence of *complications* in those individuals who received serum was much less than in untreated cases. Furthermore the mortality in the serum-treated group was decidedly lower than that observed in untreated patients. Of the 947 serum-treated patients in the hospital, 446 had no complications at the time they were admitted. In these 446 cases (Table 2), the incidence of complications was decidedly lower than in patients who did not receive serum. This is particularly significant, for the patients in the serum-treated group were classed clinically as severely or critically sick (a group in which a much higher incidence of complications may be expected), whereas the untreated patients had only a moderate or mild scarlet fever.

We have records at present of several thousand patients with scarlet fever who were treated in their homes by private physicians. Marked and prompt symptomatic and objective improvement was reported and the low incidence of complications, as well as the low mortality, has been gratifying.



TABLE 2

INCIDENCE OF COMPLICATIONS OF SCARLET FEVER AFTER CONVALESCENT SERUM THERAPY AND COMPARISON WITH UNTREATED Milder Cases\*

Day of illness when convalescent serum given.	No. of cases.	No complications.	Cervical adenitis.	Suppurative otitis media.	Rhinitis.	Arthritis.	Mastoiditis.	Nephritis.
1	24	18	3	1	0	2	0	0
2	95	77	13	5	4	2	0	0
3	129	99	15	8	6	3	1	1
4	111	91	8	6	5	2	0	1
5	57	43	9	3	3	4	1	0
6	19	17	2	0	1	0	0	0
7	6	5	1	0	0	0	0	0
8	5	4	0	1	0	0	0	0
Total	446	354	51	24	19	13	2	2
Percentage	100	79	11	5	3	4	0.5	0.5
Mild and moderately ill patients, no serum given, complications in per cent	6282	...	27	13.6	8.7	2.6	2.9	3.6

\* From Hoyne, Levinson and Thalheimer, J.A.M.A., Sept. 7, 1935.

The effect of serum on *late complicated* scarlet fever is difficult to evaluate statistically. Close observation of several hundred complicated cases in which the patients were desperately ill on admission to the hospital and were treated with serum, has convinced us that the majority of these patients have been definitely benefited by such treatment. Many patients with a septic illness have shown such definite improvement, with cessation of the progress of the disease, that we cannot help but feel that serum played an active part in overcoming the infection. For complicated scarlet fever in the late stages of the illness, we have employed massive repeated doses of serum supplemented by intramuscular injections of whole blood, or with transfusions from individuals recently recovered from scarlet fever, with increasingly better results. The value of *sulfanilamide* is discussed below.

**Diverse Streptococcic Infections.**—The beneficial effects from serum therapy in late complicated scarlet fever have been paralleled by the results in many diverse streptococcic infections. Convalescent scarlet fever serum has been used quite extensively in fulminating streptococcus infections in the last few years. In general, about 15 per cent of patients show

an excellent response, with rapid improvement and recovery. In about 60 per cent the effect of serum treatment is good, with slower but progressive recovery. In about 25 per cent, no influence is derived from the serum.

It must be stressed that successful treatment in fulminating virulent infections from the *hemolytic streptococcus* requires massive doses of from 100 to 200 cc. of serum. These may have to be repeated.

*Acute Hemolytic Streptococcic Pharyngitis.*—In acute streptococcic throat infections, with or without cervical adenitis, the response to convalescent serum is almost as specific and as striking as is seen in the treatment of early scarlet fever:

*Case I* (Fig. 12).—E. K., fourteen months old. After a low-grade temperature and coryza of one week's duration, this child was admitted to the hospital

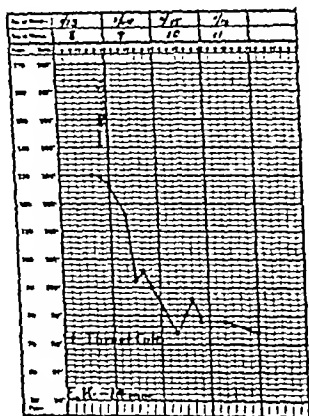


Fig. 12 (E. K.).—Acute hemolytic streptococcic pharyngitis. Treatment with 40 cc. of scarlet fever convalescent serum intravenously.

with a temperature of 104° F. The throat was markedly inflamed and edematous. Membranous patches were present over the pharynx. The child was markedly prostrated and dehydrated.

Forty cubic centimeters of convalescent serum was administered intravenously at the height of temperature. There was an immediate critical fall in the temperature which reached normal in thirty-six hours. Coincident with this fall in temperature, the toxicity disappeared and there was general improvement in the symptoms; the child made a rapid recovery and was discharged from the hospital three days after admission.

*Fulminating Hemolytic Streptococcic Pharyngitis with Septic Complication.*—This group of cases includes those in

which the onset of illness was an acute throat infection, following which one or more of the severe complications involving the cervical glands, ears, mastoid, or sinuses developed, with or without an associated positive blood culture.

In these cases, *repeated massive doses* of convalescent serum have been found necessary. Very often there is an associated secondary anemia, and in the presence of anemia whole blood from a recovered scarlet fever donor is invaluable. The clinical response in these cases is only occasionally striking, but in most instances it appears that persistent massive serum therapy is an important factor in checking the fulminating disease and in ultimate recovery.

*Case II* (Fig. 13).—V. P., aged twelve years. Three weeks before admission to the hospital this child developed an ulcerative pharyngitis with a high

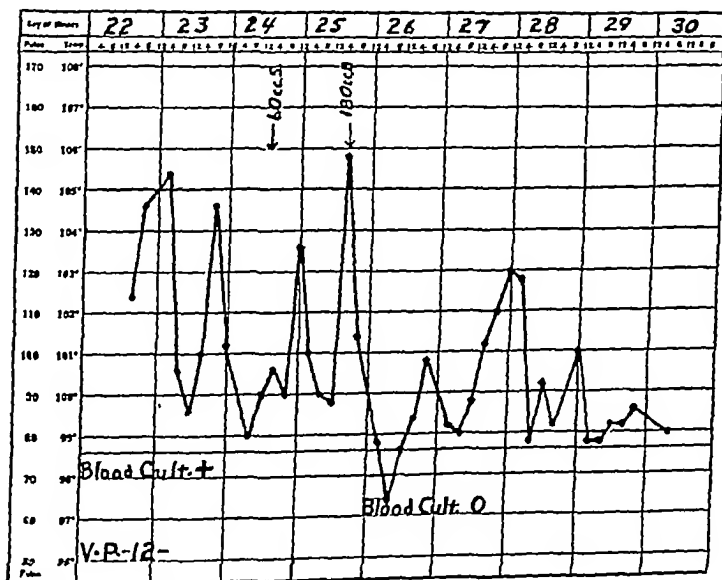


Fig. 13 (V. P.).—Hemolytic streptococcic septicemia following acute pharyngitis and cervical adenitis. Treatment with 60 cc. of scarlet fever convalescent serum intravenously and immune transfusion.

temperature. Within two days a marked cervical adenitis appeared; the gland was incised after one week but no pus was obtained. Although the adenitis gradually subsided, the septic temperature continued and, three days before hospital admission, pain in the left shoulder appeared. On admission the child was acutely ill and had a diffuse, soft, very tender swelling over the anterior left chest in the region of the second and third ribs and extending under the



dropped rapidly to normal and convalescence was interrupted only by a transient temperature rise due to retained pus in the incision of the jugular ligation. A blood culture performed fifteen days after admission was negative. The pus secured from the mastoid operations gave a pure growth of hemolytic streptococci. This child received, in all, 600 cc. of blood and 200 cc. of convalescent serum.

*Fulminating Hemolytic Streptococcic Infections with Septicemia.*—In this group of cases convalescent serum is inconstant in its effects. At times the response to serum therapy is spectacular; in most instances, however, the response is delayed and, in some cases, no effect is observed.

It is of paramount importance in these cases that at no time should *sound surgical measures* be neglected. The use of serum, as expressed by Goldberg,<sup>3</sup> is not a substitute for, but an adjunct to, sound surgery and other supportive therapy. Although distinct improvement may be observed in the patient's general condition, arrest of the illness cannot be expected until localized collections of pus are drained.

*Case IV* (Fig. 15).—F. S., aged twenty-three years. This patient was admitted to the hospital with a cellulitis of unknown etiology affecting both legs

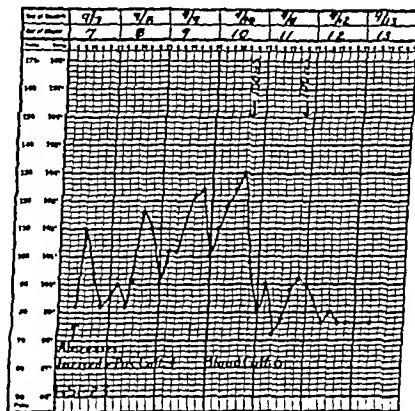


Fig. 15 (F. S.).—Fulminating hemolytic streptococcic cellulitis. Treatment with scarlet fever convalescent serum.

and a temperature of 101° F. Heat was applied and the temperature dropped to normal; the patient felt much improved and abscesses localized on the lower third of the left leg and on the upper half of the right leg. Seven days after admission these abscesses were incised under local anesthesia, with the liberation of thick pus which gave a pure growth of hemolytic streptococci. Following this incision, the temperature started to rise and, thirty-six hours later,

there was a severe chill. The following day the temperature rose to 104° F., and the patient was quite toxic and prostrated.

In the belief that a septicemia had developed, a blood culture (which gave no growth) was taken and 100 cc. of convalescent scarlet fever serum was given intravenously. There was a dramatic drop in temperature and a concomitant improvement in the clinical picture. The following day the temperature rose only to 100.2° F., but another 100 cc. of convalescent serum was given intravenously. Following this, the patient was completely afebrile, symptom free, and made an uneventful convalescence.

*Case I' (Fig. 16).—A. R., aged five years. This child's clothes caught fire and resulted in extensive second and third degree burns of the chest, back, abdomen, part of the thighs, face and arms. Tannic acid was applied, and heat, sedatives, and fluids were administered. For several days the child's con-*

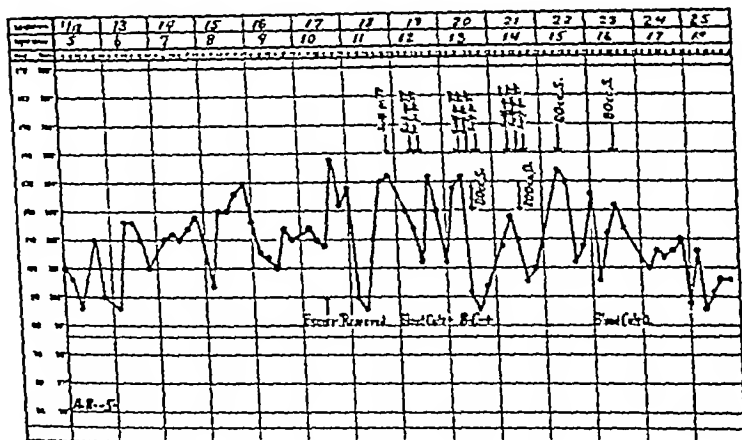


Fig. 16 (A. R.).—Hemolytic streptococci septicemia from infected burns. Intolerance with sulfanilamide. Treatment with scarlet fever convalescent serum and blood transfusion.

dition was as good as might be expected. A temperature of 100° to 103° F. persisted and the course was steadily downhill. Nine days after admission, in the belief that there was a definite cause for the maintained temperature, the tannic acid eschar was removed, revealing an extensive pus accumulation which gave a pure growth of hemolytic streptococci on culture. Irrigation of the infected areas was instituted.

The following day sulfanilamide was started, and after the child had received 90 grains of the drug, he became quite cyanotic. Since his general condition was unimproved and since two blood cultures were strongly positive for hemolytic streptococci, 80 cc. of scarlet fever convalescent serum was given intravenously. The following day the child received 45 grains of sulfanilamide and 200 cc. of blood. Again marked cyanosis developed, and the sulfanilamide therapy was stopped. Eighty cubic centimeters of convalescent scarlet fever serum was given intravenously on each of the next two days, following which the temperature gradually dropped to a relatively low level and the blood

culture became negative. Although a low-grade temperature persisted, the child made a relatively uneventful recovery.

The treatment of these cases with serum is not as specific as could be desired, because at the present time we have no reliable laboratory test to determine action of serum against a given strain of organism. In the absence of this specificity, *pooled serum*, in massive doses administered intravenously, *combined with chemotherapy*, gives the greatest hope for success. *Immunotransfusion* is a supplementary measure that should not be ignored, but it offers less specific value than massive doses of *pooled serum*.

*Sulfanilamide*.—No discussion of hemolytic streptococcal infections is complete today without at least brief mention of sulfanilamide. In our experience this drug has no definite influence on the acute course or symptoms of scarlet fever. If given early in the disease it has no influence on late complications. When *complications* do appear, however, it is of untold value, particularly for complications such as septicemia and meningitis.

It seems logical that the *combination* of serum and chemotherapy offers the ideal method of treating complicated hemolytic streptococcic infections.

#### MEASLES CONVALESCENT SERUM

The earliest work in this field appears to be that of Nicolle and Conseil in 1916. The value of measles convalescent serum was firmly established by Degkwitz in 1920. The optimal period for obtaining serum is from seven days after deferescence up to six months later. The potency of serum obtained shortly beyond this period has not been established. It is known, however, that adult immune serum from individuals who have had the disease in childhood has some value. One cc. of measles convalescent serum is about equivalent to 6 cc. of adult immune serum or 12 cc. of adult blood.

*PROPHYLAXIS*.—The major use of measles convalescent serum is in prophylaxis of the disease. Our *recommended dose* is 5 cc. for children under five years, and 7.5 cc. for children over this age. The serum should be given *intramuscularly*. When a proper dose is given within four days after exposure, most of the cases are completely protected and no disease develops. However, if the serum is administered from the fourth to the eighth day of the incubation period, in most instances a very mild atypical measles will appear. This type

of disease is called "sero-attenuated measles." Our results have shown a combined protection (either complete or partial) in 94 per cent of contacts immunized with serum (Fig. 17).

If complete protection is conferred upon the individual by the administration of convalescent serum, this protection is only *transient* because it is a passive immunity. However, if an attenuated form of the disease develops, it results in an active immunity which should be permanent. In institutions, where all contagious disease is avoided, *immediate* administra-

#### Measles Immunization in Relation to Date of Serum Inoculation



Fig. 17.—Measles contacts treated with measles convalescent serum. Relation of results to number of days of incubation before serum administration.

tion is practiced to obtain complete protection; in the home, on the other hand, where an active immunity is more desirable, *delayed* administration is recommended.

As may be seen in Fig. 17, the dose required is definitely related to the duration of incubation at the time of inoculation. The virus is presumably multiplying, so that for each additional day of incubation, a progressively larger dose of serum is required to achieve complete protection or sero-attenuation. If the incubation period is passed and the child is in the pre-eruptive stage, the dose required is quite large.



**Treatment.**—Measles convalescent serum has been used successfully in the treatment of a series of sick children who inadvertently developed measles. Serum was administered during the pre-eruptive stage, the diagnosis being made on the finding of Koplik spots as well as prodromal symptoms. The dose of serum was 50 cc. intravenously. A definite therapeutic effect was observed. The temperature fell and, on the eruptive day, was usually under 101° F.; in some instances it was

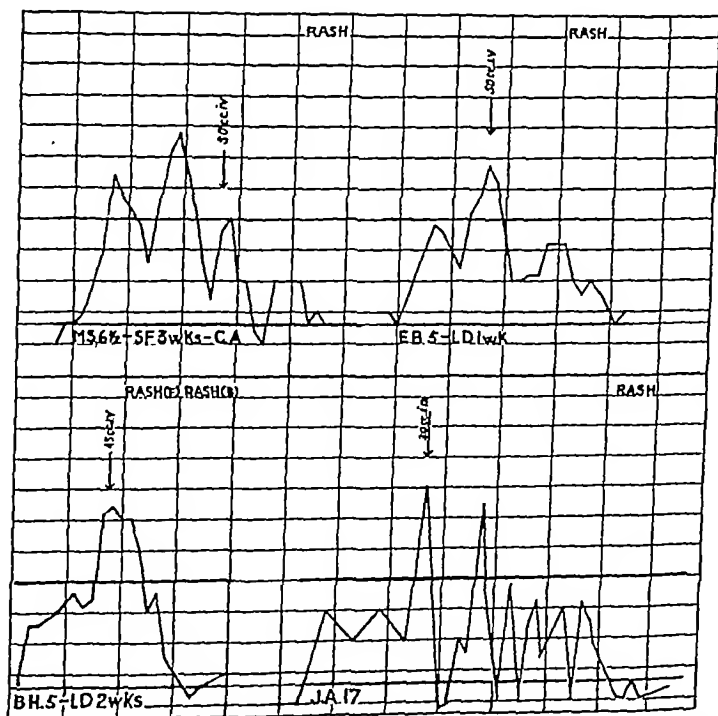


Fig. 18.—Four patients treated with measles convalescent serum (30 to 50 cc intravenously) in the pre-eruptive state (Koplik spots) of measles.

normal (Fig. 18). The cough and prostration decreased markedly. In 70 per cent of the cases the eruption was pale, discrete and atypical like the eruption seen in sero-attenuated or modified measles.

*Placental extract*, which apparently is the concentrated globulin fraction of adult immune serum, is effective in measles for the same reasons as convalescent or adult immune serum. The reactions observed from the product may be due to its

method of preparation. for placental contamination is inevitable and, although the material is rendered sterile, reaction producing bacterial products may be present.

#### POLIOMYELITIS CONVALESCENT OR IMMUNE SERUM

Poliomyelitis immune serum is obtained from donors who have recovered from the disease within the preceding ten to fifteen years. This time is probably not optimal and is employed only because most cases occur in children and a considerable time elapses before an appreciable amount of blood may be safely withdrawn. The dosage employed is therefore larger than with the real convalescent serum.

The value of this serum is at present a highly controversial subject. Many impressive authorities feel it is valueless and general medical opinion is very guarded. Nevertheless, we have used this serum extensively for the last ten years because the results have been so encouraging.

**Treatment.**—Our method of treatment differs from that employed elsewhere. We employ *very large doses* intravenously, from 100 to 250 cc., depending on the age, as an initial dose and routinely repeat the serum every twenty-four hours in the average case and every twelve hours in the critical or fulminating case until the infection subsides. Some patients have been given as much as 1200 cc., and the *average* dose has been 300 cc.

Up to the present time almost 400 patients have been treated with serum in the preparalytic stage. The incidence of moderate paralysis in this group is under 4 per cent, and it is rare for severe paralysis to appear if serum treatment was started early in the disease.

Serum is also used in paralyzed patients if they are seen during the acute stage and paralysis is spreading. Statistical analysis here is fruitless, but it is our distinct clinical impression that progression of paralysis is in most instances checked, and that subsequent muscle recovery is more rapid and more complete than in paralyzed patients who had received no serum.

Unfortunately there is no control untreated group for comparison, and the disease is so variable in its incidence and severity of paralysis that our results, although very encouraging, do not constitute absolute proof of serum efficacy.

#### MUMPS CONVALESCENT SERUM

The earliest work in this field was by Hess. The literature, however, is scant. Most investigators report obtaining their

serum up to about one month following defervescence. We have used serum up to six months from the date of onset of illness and find it of value.

Much more study of mumps convalescent serum is required. Its relative strength compared with adult immune serum is unknown.

**PROPHYLAXIS.**—Although successful results have been reported with smaller doses, we believe that 20 cc. should be the *minimal dose* employed, at least for susceptibles who by virtue of prolonged and intimate contacts at home tend to show a higher attack rate.

Our results in 186 such home contacts are as follows: Of twenty-three patients who received 10 cc. of serum, four or 19 per cent developed mumps. Of 157 patients given 20 cc. of serum, ten or 8 per cent developed the disease.

Only the number receiving 20 cc. of serum is therefore large enough to warrant any consideration. Although the results are not impressive, nevertheless in view of the circumstances that all these patients were home susceptibles, intimately and continuously exposed, there is some justification for the feeling that some benefit was derived from the serum.

**Treatment.**—Our own observations are too few to be of significance. The scant literature suggests that the disease itself is rendered milder by serotherapy.

Of far greater importance is the favorable effect of serum administration on the incidence of *complications*. The best study has been submitted by DeLavergne and Florentin who treated 113 patients with 20 cc. of serum and, after five days, administered an additional 10 cc. The reduction of orchitis from 24 per cent in untreated controls to 4 per cent in the serum-treated cases, and of "meningitis" from 8 per cent to 1½ per cent, is impressive and supports the view that convalescent serum has therapeutic value. Probably a dosage of 40 cc. is advisable for therapy in adults.

#### CHICKENPOX CONVALESCENT SERUM

The initial and favorable report of Blackfan *et al.* has been followed by publications both favorable and disappointing. The optimal period for obtaining the blood is not established. Presumably it should be obtained immediately after the patient has recovered. According to Gordon and Meader serum obtained after a lapse of 3 to 4 months has little value. Lewis and Barenberg have found adult serum worthless.

**PROPHYLAXIS.**—Our own experience with the use of con-

valescent serum derived from recently recovered donors has been encouraging. Although consistent protection is not frequently achieved, the character of disease is extremely mild, and the extent and number of lesions very limited. We also found adult immune serum of highly questionable value, even in 40 cc. doses for infants and children.

Until further study, the value of chickenpox convalescent serum for prophylaxis remains problematical.

#### PERTUSSIS CONVALESCENT SERUM

Since Bleyer's first disappointing report in 1917 on the use of pertussis convalescent serum in active therapy, there have been many additional publications pointing to a relative effectiveness from this agent as a *prophylactic* measure. The scarcity of adults who develop pertussis and can act as donors limits the practical value of this agent.

The more recent work of Kendrick, and of McGuiness, Bradford and Armstrong, opens a new field of therapy with hyperimmune human pertussis serum. Their results not only point to a prophylactic value, but also to *therapeutic* efficacy from the administration of this agent. If adult volunteers for hyperimmunization can be enlisted, the problem of supply of an effective serum may be solved.

#### MISCELLANEOUS CONDITIONS

There are a host of infectious diseases that have not been studied from the viewpoint of the value of human convalescent or immune serum. The appended bibliography also demonstrates a variety of diseases in which some success has accompanied the use of serum. The studies are, however, inadequate and there have been no or few attempts to investigate further and confirm the findings.

With the development of organizations and intensifications of efforts towards human convalescent serum collection, it is hoped that this field of human serotherapy will be thoroughly and systematically probed to evaluate the serum for each disease and standardize the best methods of preparation and treatment.

#### HUMAN SERUM AS A BLOOD SUBSTITUTE

Human serum has applications other than as a specific anti-serum against infectious diseases. There has been a rapidly increasing use of human serum as a nonspecific agent in *acute infections*, as a temporary emergency measure in sudden se-

*vere hemorrhage*, in *shock*, in *burns*, and in those states producing *hypoproteinemia*. Human serum is effective in these conditions because of its protein content and colloid nature.

The *advantages* of human serum transfusions are the ability to prepare the serum beforehand and store it for long periods of time without deterioration; transportation without ill effects and with no great difficulty; rapid availability and simplicity of administration; no necessity for time-consuming blood matching tests; and freedom from reactions.

The value of serum or plasma is especially advantageous for those institutions which possess a *blood bank*. Outdated preserved blood no longer need be discarded. The supernatant plasma may be recovered and, if not contaminated, can be stored and utilized as a blood substitute.

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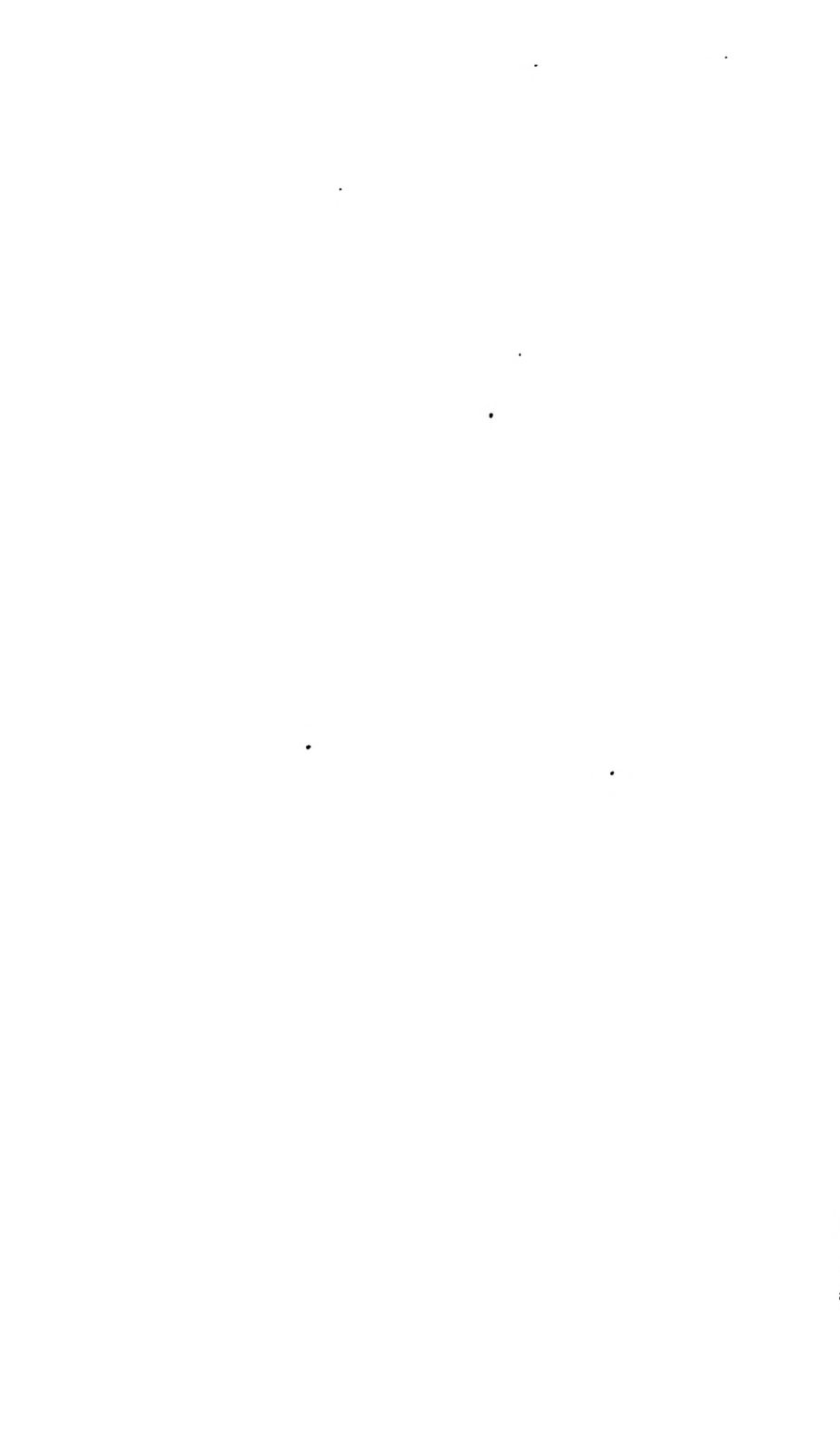
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CHRONIC PRIMARY DISEASES OF THE LOWER FEMALE  
URINARY TRACT

*Gentlemen:* The discussion this morning concerns an everyday problem which has long been misunderstood or perhaps just overlooked by clinicians. This rather considerable group of female patients is seen at first not by the urologist, but usually by the general practitioner, internist, or gynecologist. Women complaining of a long established, irritable bladder syndrome consisting of frequency and burning on urination with perhaps pains in the groins or back, formerly may have been given some "cystitis" tablets accompanied by repeated bladder lavages, depending upon the patient's response to therapy. Such patients were assumed to have an inflammation of the bladder.

This reasoning has been shown to be in error. In reality the patient's symptoms of irritable bladder, usually with normal urine, are caused chiefly by pathologic lesions in the urethra. In the order of their frequency these urethral changes are chronic granular urethritis, polypoid formations and cystic masses in the proximal portion of the urethra, stricture of the urethra of large or small caliber, urethral caruncle, and fibrosis of the bladder neck, comparable to that seen in the male and urethral diverticulum. Because of the direct relationship of these lesions to each other, seldom is one encountered without the association of one or more of the others.

Do not assume, however, that the symptoms of irritable bladder are caused *solely* by urethral changes, for disease of the bladder wall, including Hunner ulcer or elusive ulcer, stone in the bladder or a tumor, may be the underlying disturbing factor. It must be remembered that studies of the upper

urinary tract in these patients have been made chiefly with the aid of excretory urograms. The most significant and extensive kidney damage occurred in those patients who had obstruction (fibrosis) at the bladder neck. Relatively little renal change was found in patients afflicted with chronic urethritis, stricture and elusive ulcer.

#### CHRONIC GRANULAR AND CICATRICIAL URETHRITIS

*Case I.*—Our first patient is a young woman twenty-eight years of age. She has been married two years and has always taken careful steps to avoid pregnancy. Her chief complaint is frequency of urination up to every hour during the day, but she does not get up at night. Some burning and urgency is present at times. She feels well and has no other complaints.

The clear voided urine reveals an occasional pus cell, nothing more. In examining this patient we will note particularly the *vaginal introitus* and the *urethral meatus*. Routinely we take smears from the vaginal secretions, to be examined wet for *Trichomonas* infestation and dry with methylene blue or Gram's stain for yeast (*Monilia*) and the *gonococcus*. This patient is negative for all. Often chronic, recurrent nonsuppurative urethritis may be perpetuated by these vaginal changes caused by yeast and the trichomonas. The gonococcus, in our experience, has not caused such chronic urethritis. Next *Skene's glands* on either side of the urethra are milked and the secretion, if any, studied.

The urethra is now being calibrated with olive-tipped sounds, the so-called acorn sound. The diagnosis of *stricture* is made by feeling the resistance offered on withdrawing the sound, not by the feel of the sound upon introduction into the urethra. The female urethra is just 3.5 cm. long, so care must be exercised not to traumatize the bladder. The normal female urethra should readily allow the passage of a No. 26 F. sound.

You will notice that this No. 22 F. acorn sound hangs definitely in the mid-urethra and a bit of blood is produced. The No. 24 F. *Brown-Buerger cystoscope* enters the urethra with definite resistance. One sees the bladder to be negative, but the internal urethral orifice is injected and seems roughened. The cystoscope is withdrawn. Inspection of the entire circumference of the urethra is allowed by this water-dilating urethroscope as it is withdrawn. I know of no other instrument giving so complete a view around the urethral walls. The whole urethra presents an irregular cobblestone, reddened

appearance with interspersing whitish bands in mid-urethra, the cicatricial result of inflammation.

**Treatment.**—Treatment of patients of this type usually is rather simple. We will depend upon *gradual dilatation* of her urethra with male type sounds, starting as a rule perhaps with 21 F. twice a week. Each dilation will be accompanied by the instillation in the bladder and urethra of a few cubic centimeters of a strong silver salt, preferably 0.5 of 1 per cent *silver nitrate*. Usually at the end of from four to six weeks the urethra can comfortably take a 27 F. or 28 F. sound, and sometimes 30 F., depending upon the patient's tolerance.

We will follow this woman's progress, and even after she is comfortable, will dilate her urethra at perhaps monthly intervals to make certain the urethra remains open.

**Question:** Is it ever necessary to do more in the treatment of these patients?

**Answer:** Yes, occasionally relief is obtained only after all the granulations are lightly but thoroughly electrocoagulated over the whole surface of the posterior urethra, proximal to the sphincter.

**Question:** What causes such a chronic urethritis?

**Answer:** Probably infection arrives in the urethra from the exterior. Why it should persist is not quite clear. One belief is that true gland structures exist in the proximal portion of the female urethra analogous to the prostatic glands in the male. These glands might harbor infection, producing the local findings. Another theory holds that true glands do not exist in the female urethra, but that the changes are represented by liquefaction of the centers of solid intra-epithelial cell nests or ramifying mucosal crypts. In our experience, recurrence of symptoms is more frequent in the presence of a resistant vaginal infection which acts as a neighboring focus.

**Question:** Does this disease occur in children?

**Answer:** Many believe that it does very definitely, with about the same clinical and pathologic picture. The only added clinical feature, however, is that of *eneuresis*. Some investigators have found urethral lesions in over a third of female children suffering from *eneuresis*. The general treatment in children follows that in adults.

**Question:** Is the eradication of yeast and *Trichomonas* vaginitis strictly essential to the relief of bladder symptoms? Does this vaginal infection *per se* cause urinary disturbance?

**Answer:** We have found in many patients a thin, semi-transparent cotton-wool membrane covering all or part of the



trigone and bladder neck in the presence of *Trichomonas* vaginitis. Rarely does the vaginitis alone upset the bladder function, for in most instances various changes in the urethra are the immediate cause. However, recurrence of the vaginitis, which is especially prone to happen with *Trichomonas* infestation, may lead to exacerbation of the frequency and burning on urination. Controlling the vaginitis relieves the urinary symptoms in these patients.

#### POLYPS AND CYSTS OF THE URETHRA

Polyps and polypoid or cystic masses accompany granular urethritis in about three-quarters of our cases. Most of these masses lie about the immediate bladder neck and may project back into the bladder, or they may be found even 1 or 2 cm. distal to the bladder in the region of the urethral sphincter, so that they disturb sphincteric action even to the point of causing actual incontinence. Rarely do these polyps grow to a large size. We will present instances, however, in which the polyps attained relatively large dimensions.

*Case II.*—This next young woman is also twenty-eight years of age. She is unmarried and gives a negative venereal history. Her chief complaint is frequency of urination during the day (as often as every twenty minutes). She states she feels like urinating most of the time and that voiding never completely relieves her. In fact, for the past six years she has been unable to attend weddings, funerals, or the movies because of this inconvenience. The striking thing is that she voids at most only once a night. It is characteristic of urethral lesions that they do not cause constant nocturia, whereas lesions of the bladder, especially elusive ulcers, are generally accompanied by the symptom of nocturia.

This patient's general condition is excellent. The urine is reported grossly clear, with an occasional erythrocyte and white blood cell. No changes have been found in her cardiovascular or nervous system.

*Treatment.*—Our anesthetic is 4 per cent *cocaine* on a thin cotton-covered wood stick. You will notice that this acorn 24 F. sound meets some resistance at the bladder neck or proximal urethra. The cystoscope enters without meeting obstruction. The bladder reveals no changes except the presence of at least half a dozen rather large, semitransparent polypoid masses about the bladder neck. One or two of these polyps are in the region of the sphincter about 1.5 cm. out in the urethra (Fig. 19). Each cyst or polyp has at least one blood vessel entering it. The urethral mucosa between the polyps is rather granular. We will substitute a *panendoscope*

for the cystoscope and fulgurate the polyps. Those of you near by can hear the muffled explosion as they pop when touched with the current.

This patient will be kept quiet in bed for twenty-four hours. We will make another cystoscopic examination in a few days because frequently the sloughing of the polyps after fulguration releases or exposes other adjacent polyps, all of which must be removed. Note the absence of bleeding or pain. (*Note.*—It was necessary to fulgurate one or two secondary polypi later. Relief of frequency was dramatic. Several dilations a month later revealed an increased urethral caliber



Fig. 19.—A, Small polyps at the bladder neck. B, Large, more pedunculated polyps in the urethra at some distance from the bladder.

of F. 27 and this was extended gradually to F. 30. The patient's social program was restored completely.)

*Case III.*—This next patient is a Negro woman thirty-two years of age. She was referred by the gynecology clinic for cystoscopy to determine the status of the urethral sphincter before urethroplasty for incontinence of five years' duration. Following the birth of her last child this patient was unable to hold her urine and has been wearing cloths and towels since.

Examination at the time of admission revealed slight cystocele, with two urethral fistulae on either side in the distal 2 cm. of the urethra. Two huge, well organized polyps resembling stalactites projected downward from the roof of the urethra in the region of the sphincter, holding the sphincter open. These were destroyed by *fulguration*.

Now she states she rarely loses urine and then only when her bladder gets too full. The result is more than we expected because the well organized bases of the polypi required deep

coagulation into the region of the sphincter fibers, possibly weakening the muscle.

The next patient is our last one to exhibit urethral polypi:

*Case IV.*—This patient is thirty years old and single. As you will notice, there are three large, discrete, slightly injected tumors projecting from the urethral meatus. The bases of all three are well within the urethra and the pedicles are long. The largest polyp is about 1 cm. in diameter (Fig. 20). These polypi present an entirely different appearance from urethral caruncle,

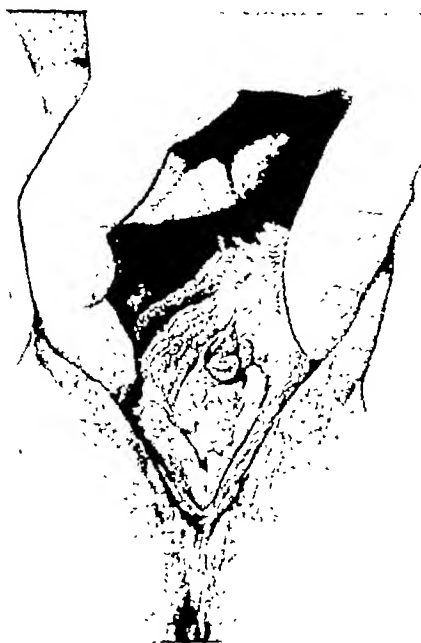


Fig. 20.—Three large, discrete polyps which are attached by long pedicles well within the urethra, projecting from the meatus like a cluster of grapes.

which is usually more livid in color, with a broad base. They are causing her symptoms of frequency, some difficulty in urinating and discomfort on sitting. Cystoscopy does not show any bladder or internal urethral changes.

The polypi are too large to fulgurate so we will remove them by *sharp dissection*, using as anesthetic injections of 1 per cent novocain around the several pedicles. You see, the base of one continues to ooze in spite of packing. It is controlled by a small through-and-through suture. After healing has occurred, the urethral meatus will be dilated to insure its patency.

(Note.—A year later this patient returned with a recurrence of one polyp almost as big as before. This was tied off as close to the base as possible with a catgut ligature. When we were through she said she intended marrying again in two days and would go through the ceremony, but that would be all for the time being. The polyp sloughed off in four days, leaving a clean base which was touched with 10 per cent silver nitrate.)

### STRICTURE OF THE URETHRA

Calibration of the female urethra should be regularly carried out as part of the investigation of the female urinary system, for stricture in this organ is a very important lesion and is unrecognized all too frequently. The mere passage of an instrument of uniform diameter gives insufficient evidence of narrowing of the urethra. The *olive-tipped acorn sound*, which was previously demonstrated, must be employed for this purpose. The stricture may be of small caliber, actually causing extreme difficulty in urinating, or of large caliber, with less pronounced symptoms of obstruction. These women may have bizarre backaches, which in the past have been blamed on the presence of stricture in the ureter; but their backaches can be explained far more often by the pathology found in the urethra.

Seldom do we encounter so dense a stricture in the female urethra as that presented by this next patient:

*Case V.*—This Negro woman is twenty-four years of age. She had one child before contracting gonorrhea at the age of twenty-two. After a stormy pelvic infection a residual pus tube was removed elsewhere. She does not recall having had bladder treatment at any time. Difficulty in urinating appeared gradually about a year ago. Diurnal and nocturnal frequency about every two hours has been established about six months. The urine is quite loaded with pus, but chills and fever have not occurred.

You will recall that this patient was presented briefly at the previous clinic. At that time we were not able to pass the ordinary sounds into the urethra and finally succeeded in passing with difficulty a filiform guide attached to a No. 10 F. hollow LeForté sound. Six ounces of residual urine were found. The densest portion of the stricture lay in the mid-urethra, the most common site for stricture in the female urethra.

Someone proposed then that we study this case exactly as we study the male who has bladder neck obstruction, *i.e.*, carry out tests of kidney function and visualize the upper urinary

tract to determine the amount of kidney damage done by the backing up of urine from the obstructed bladder. The findings were as follows: phthalein output after intravenous injection of the dye, first half hour 30 per cent, second half hour 20 per cent, and second hour 15 per cent—a total of 65 per cent—which represents a fairly normal excretion curve. Excretory urograms taken after the intravenous injection of 30 cc. of diodrast revealed a slight decrease in initial concentration of the dye in the kidney pelves, which were moderately but definitely dilated. The ureters also were definitely dilated. The bladder was slightly irregular, the picture presented by a bladder undergoing compensatory hypertrophy in overcoming obstruction.

**Treatment.**—This woman was therefore unquestionably on her way toward serious damage to her kidneys by back pressure. We will continue to dilate the urethra slowly and, if she cooperates, she should recover completely.

**Question:** What percentage of clinically diagnosed strictures of the female urethra are caused by gonorrhea?

**Answer:** Very few, as contrasted with the male, and these are more often of the small caliber variety. Nonspecific urethritis undoubtedly is the forerunner of many strictures of large caliber, *i.e.*, arbitrarily strictures which produce obstruction to a 20 F. or 22 F. acorn sound. The proximity of the urethra to the vagina increases the hazard of infection, with ultimate stricture formation, from nonspecific organisms in the vaginal tract incidental to the carrying out of the functions of the vagina. Trauma may also occur to the urethra during childbirth or with various operative procedures on the urogenital tract, such as vaginal hysterectomy, cauterization of the cervix, or fulguration of urethral caruncle. We have not seen stricture of the female urethra after severe pelvic injuries, because the short urethra in the female is seldom torn as it is in injuries of the male pelvis. Stenosis of the urethra may result from the extended use of radium previously applied to the cervix. It must always be borne in mind that any persistent obstruction in the urethra requires complete investigation to rule out fibrosis of the bladder neck and neoplasm, which may be primarily urethral or an extension of an infiltrating bladder tumor located near the bladder neck.

The more common *complaints* associated with urethral stricture are frequency during the day with often mild nocturia, and vague lower abdominal and back pains. Urgency and dribbling may accompany pronounced urethritis and

trigonitis. We are presenting the next patient because she had a narrow urethra. The treatment of this large caliber stricture alone relieved discomfort over the right kidney and right lower quadrant which had been explained elsewhere on the basis of a ureteral stricture.

*Case VI.*—When this forty-two-year-old woman presented herself at the clinic, her terse statement that she came to have her right ureter dilated again was accepted with a little friendly curiosity. She said the manipulation always relieved the pain in her right lower quadrant and back and that the accompanying mild frequency and burning disappeared. Then she would be comfortable for a few months.

Examination revealed the urine to be negative. Abdominal palpation disclosed nothing of interest. Calibration of the urethra with acorn sounds uncovered a narrow region in the mid-urethra producing a hang to a No. 22 F. bougie à boule. The bladder was essentially normal. The urethra was granular. The ureters were not catheterized, yet she obtained relief from her abdominal and back pains upon dilating the urethra up to 30 F. in several sittings. Perhaps merely the passage of the cystoscope through the urethra incident to dilating the ureter in many so-called strictures of the ureter provides the unrecognized therapeutic measure of value in these cases.

Do not forget that careful urethroscopy and cystoscopy are necessary to *differentiate* stricture of the female urethra from the more complicated and often more serious lesions of fibrosis of the bladder neck and neoplasm, both of which defy simple therapeutic measures.

#### DIVERTICULUM OF THE URETHRA

One does not encounter many diverticula of the female urethra. Some are probably congenital. We have apparently encountered only the acquired type. Two patients will be presented who undoubtedly acquired their diverticula following specific pelvic and urethral infections. In the first case a peri-urethral abscess ruptured into the urethra, resulting in diverticulum formation. The second patient acquired her diverticulum differently, because it formed between two strictures of the urethra as a result of back pressure of urine. Gonorrheal urethritis preceded the strictures.

Textbooks on urology suggest regularly that diverticulum of the female urethra be removed surgically. The following two patients are presented because they were treated adequately by *nonsurgical* means:

*Case VII.*—This woman is forty-eight years of age. Her medical history extends back many years. She first entered the hospital eleven years ago at the age of thirty-seven. Her complaints at that time were frequency of urination and some burning with occasional dribbling which had been present intermittently and with varying intensity for many years. Her difficulties began when she contracted a Neisserian infection in her twenties. A peri-urethral abscess resulted, which ruptured spontaneously into the urethra.

Cystoscopy and urethroscopy eleven years ago revealed an opening about  $\frac{1}{4}$  cm. in diameter on the posterior wall of the urethra slightly to the left of the midline. This opening was about 2 cm. distal to the internal urethral orifice; several small polypi were present about the bladder neck. A No. 5 ureteral catheter was threaded into the opening 12 cm. before resistance was encountered. Then 4 cc. of a 15 per cent solution of sodium iodide introduced into the catheter revealed roentgenographically the extent of the diverticulum (Fig. 21, A). Urine cultures were sterile although 20 pus cells per field were present.

This patient refused operation for removal of the diverticulum. The polypi were removed by electrocoagulation. The

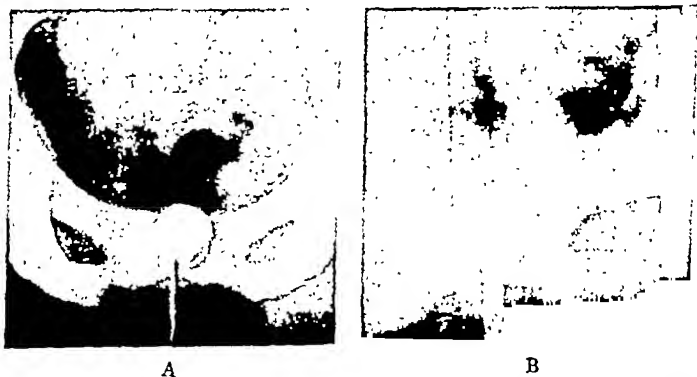


Fig. 21.—A, Urethral diverticulum visualized by injecting contrast media through a ureteral catheter coiled in the sac. B, Urethral diverticulum visualized by injecting contrast media through a urethral catheter lying just within the urethra.

urethra was dilated up to 28 F., the diverticulum emptied occasionally of catarrhal discharge by vaginal pressure, and mild silver protein solution was instilled. Now you heard the patient say, eleven years later, that she no longer has urinary symptoms although she still has her diverticulum.

Our next patient with a urethral diverticulum has kindly consented to appear before the clinic:

*Case VIII.*—This patient first entered the hospital eighteen months ago at the age of thirty-four. Her chief complaints were frequency and nocturia (from 5 to 6 times), with the sensation of a lump in the right lower quadrant

and dull, aching pain in the lower abdomen and back practically all of the time. The symptoms all began about the time of her marriage seven months previously.

You will notice the low midline scar, resulting from an operation for removal of the right tube and appendix five years ago during a specific pelvic infection. At the first cystoscopic examination, the instrument met considerable obstruction in the proximal portion of the urethra. A cotton-wool, false membrane covered the trigone. *Trichomonas vaginalis* vaginitis was found. Two strictures were present in the urethra with a diverticulum lying between them, the opening of which was about 1.5 cm. in diameter. The urine contained a few pus cells and revealed *Staphylococcus albus* on culture. This pocket was visualized by injecting 4 cc. of 50 per cent diodrast through a urethral catheter placed in the urethra (Fig. 21 B). The kidneys were normal radiographically.

In view of our experience with the previous patient, this woman was treated conservatively. She states that the frequency and nocturia soon disappeared and the sense of fullness in the lower abdomen slowly was relieved, as normal urinary function was restored. The strictures in her urethra were slowly dilated beginning with a 22 F. sound. Now a 30 F. sound enters the urethra with ease.

**Question:** In view of the results obtained in these two cases, why is surgery advised for urethral diverticulum?

**Answer:** Some diverticula attain a much larger size than those presented, causing annoying dribbling and the two-stage type of urination when the filled diverticulum empties after the bladder is emptied. If the urethras of patients with diverticula were adequately treated, very few would require surgical intervention. Probably the larger the urethral opening of the diverticulum, the better the drainage, thereby increasing the chances of success of conservative measures in relieving the symptoms of these patients.

#### CARUNCLE OF THE URETHRA

Exceeded in frequency only by papillomas and polyps at or near the bladder neck, caruncle at the urethral meatus is the next most common benign tumor in the female urethra. Usually caruncle is accorded first place, simply because intra-urethral polyps have escaped either observation or recognition.

**Case IX.**—Our first patient presenting urethral caruncle is fifty years of age. She was referred by the Department of Gynecology, where she first pre-



sented herself because of vaginismus, lower abdominal pains and backache. Her rest at night was increasingly disturbed by discomfort in the bladder region, especially on urination. Occasionally bloody spotting of her clothing occurred.

Now this patient's symptoms are about the most pronounced and characteristic of caruncle that one might wish. However, other patients are observed with caruncle who have a physical appearance not unlike this patient's, yet who experience no subjective symptoms. You will notice how the urethral meatus is located deeply in the anterior vaginal wall, exposing it to trauma during cohabitation. The cystoscope enters with some difficulty. Manipulation produces some bleeding at the bladder neck. No polyps are seen. The urine contains a rare pus cell.

It might be added that several polyps in the proximal urethra were fulgurated by us several years ago, at which time nothing was found at the meatus.

**Treatment.**—Owing to the deep-set urethra we are having difficulty retracting the lips of the meatus, so that the normal tissues adjacent to the caruncle will not be burned. The caruncle protrudes from the posterior lip and is firmly attached by a broad base. The moist, beefy appearance is rather characteristic. We could not touch it, probably, without the help of the 4 per cent cocaine anesthetic application. If this caruncle were any larger or the base indurated, sections would be taken on suspicion of malignancy.

The fulgurating electrode tip is carefully applied to the caruncle, slowly coagulating it thoroughly. Seldom does bleeding occur, and then chiefly when the burned tissue sloughs later. Occasionally *repeated electrocoagulation* is necessary. This patient will be followed carefully until the meatus is healed, when the urethra will be gently dilated to assure its adequate patency. (*Note.*—Within a week this patient stated she felt more comfortable and rested better than she had for months.)

**Question:** Is caruncle related to gonorrheal infection?

**Answer:** We have no evidence of such a relationship.

**Question:** Is the histologic appearance of caruncle characteristic?

**Answer:** Unless the origin of the tissue is known, the microscopic picture of caruncle is hardly distinctive. The term "caruncle" merely means a naked, fleshy excrescence. The tumor is composed largely in some instances of newly formed dilated blood vessels interspersed with leukocytes and covered

with transitional epithelium showing metaplastic changes, considered the result of inflammatory changes. These epithelial changes with infoldings at times suggest malignant changes, although we can present no definite personal evidence that true caruncle undergoes malignant degeneration, a condition, however, which must ever be kept in mind in these cases.

#### FIBROSIS OF THE BLADDER NECK

In the male, fibrosis or contracture of the bladder neck has assumed an important place in the field of urology. It is not yet widely recognized that fibrosis of the bladder neck in the female is just as important and even more deadly, because at least in the male everyone usually thinks of some form of bladder neck obstruction in the presence of symptoms of "prostatism," while only too often the troubles of the poor female sufferer with chronic bladder dysfunction are blamed on a cystocele, relaxed sphincter from birth trauma, or some other pelvic pathology.

Fibrosis of the bladder neck in the female *is not rare*. In the past six months alone this lesion has been found, and proved at operation, in about 0.5 per cent of all the patients observed cystoscopically by us. Like many other things, *to think* of something is to find it. Not so long ago, one of us (R.H.H.) attended a large section post-graduate assembly. During the clinicopathologic conference the protocol of a middle-aged female patient was presented. Only the final pathologic diagnosis was withheld. She had apparently died of renal damage, and from her long-standing history of frequency, dysuria and only recent difficulty urinating, we suggested fibrosis of the bladder neck, which proved to be correct. The excellent pathologist in attendance admitted after all the facts were correlated that he had never before fully appreciated the clinical picture of chronic renal damage in the female due to back pressure from an obstructed, fibrosed bladder neck. Of course he had observed the lesion many times, but the implications of the condition had not been apparent.

The importance of the fibrotic bladder neck is reflected in the extensive but often subtle *renal damage* caused by back pressure. The bladder is trabeculated to various degrees, and residual urine may be great owing to decompensation, or small in the presence of compensatory hypertrophy of the bladder wall. A simple cystogram made by introducing contrast media through a urethral catheter reveals the trabeculated bladder by its irregular, often serrated, outline. At times

definite diverticula form in the bladder due to pressure. The diagnosis is completed only by *cystoscopy*.

May we have the next patient, who presents an excellent example of fibrotic bladder neck, stone in the bladder secondary to the obstruction, and severely damaged and infected kidneys due to back pressure of urine.

*Case X.*—This patient is thirty-five years of age and is the mother of five children, the eldest being eighteen. She entered the Gynecologic Clinic five years ago because of frequency and dribbling of urination, but she did not return for urologic investigation until a few weeks ago because of increased bed wetting and an attack of acute retention requiring catheterization. She passed blood afterward for five weeks and had two separate attacks of chills and fever.

Examination on admission revealed her bladder distended half way to the umbilicus. Cystoscopy revealed 350 cc. of residual urine, which contained pus (grade 2), with hemolytic streptococci on culture. The heavily trabeculated bladder held a dark-colored stone, 2.5 cm. in diameter, which did not show in the plain radiogram. The bladder neck was irregular and generally contracted.

The retrograde cystogram showed an irregularly outlined, trabeculated bladder (Fig. 22 *A*), while the film taken after the medium was drained off showed the negative outline of the bladder stone (Fig. 22 *B*). No reflux of dye up the ureters



Fig. 22.—*A*, Retrograde cystogram showing a contracted, irregular trabeculated bladder with deep cellule formation. The normal bladder outline is smooth. *B*, Cystographic media drained off, showing negative outline of bladder stone, which failed to show in the plain roentgenogram.

occurred, but kidney damage was severe, because on excretory urography the left kidney hardly visualized at all, and the right kidney pelvis was greatly dilated (Fig. 23). The blood NPN was 36 mg. per cent. Wassermann and Kahn reactions were negative.

The bladder stone was crushed with the blind lithotrite and the bladder neck resected transurethtrally under sacral anesthesia. It was necessary to resect the bladder neck further six days later, after which she had no residual urine, her stream was free, and the nocturnal dribbling ceased. The stone was made up of ammonium urates and a trace of calcium



Fig. 23.—Same case as in Fig. 22. Excretory urogram revealing delayed visualization in the hydronephrotic left kidney, with better function in the hydronephrotic right kidney. The hydronephrosis is due to bladder neck obstruction.

phosphate. Her control is now perfect, a month after operation, and she seems a different person.

The next patient is being shown because she again presents in its entirety the syndrome of long-standing bladder neck obstruction due to fibrosis with resulting diverticula of the bladder and chronic pyelonephritis due to back pressure from the bladder:

*Case XI.*—This patient is now forty-six years of age. It is five years since we resected her bladder neck for fibrosis. She returns occasionally for a

check-up of her residual urine, which is zero, and to calibrate the urethra. Not one attack of pyelonephritis has occurred since the operation.

At the time of her admission, five years ago, she complained of urgency, frequency and difficulty in starting her stream since childhood. She never felt as though she emptied her bladder. During high school an attack of acute retention occurred, which was relieved by hot baths. Repeated attacks of chills and fever with left pyelonephritis occurred during the five years before we first saw her. A therapeutic abortion had been done during that time on account of the kidney infection.

Examination of her urine revealed pus (grade 4), with *Escherichia coli* cultured from the left kidney. Four ounces of residual urine were present. The bladder was quite trabeculated and the median segment of the bladder neck elevated.



Fig. 24.—A, Retrograde cystogram in the presence of fibrosis of the bladder neck revealing diverticula arising from either side of the bladder. B, Some media is retained in the larger diverticulum after bladder is emptied.

A retrograde cystogram revealed diverticula arising from either side of the bladder (Fig. 24 A). No ureteral reflux occurred. After emptying the bladder, a slight amount of media was retained in the larger right-sided diverticulum (Fig. 24 B). Excretory urograms revealed slight dilatation of the left renal pelvis. Fever at times rose to 104° F. when the retention catheter was removed. Neurologic examination was negative.

Resection of the median portion of her bladder neck opened it widely. Within a week, residual urine was 10 cc. Upon release from the hospital this patient felt better than she had in years and was voiding freely for the first time. Her pyelitis has not recurred in five years now, because the obstruc-

tion at the bladder neck, which kept her bladder infected and forced the infected urine up to the kidneys, is gone.

The next four cases will be just briefly presented. Transurethral bladder neck resection was performed on three patients because of long-standing symptoms of bladder outlet obstruction; the fourth patient refused operation.

*Case XII.*—The first woman is seventy-seven years of age. For ten years she has had frequency of urination, nocturia up to ten times, with urgency and burning. The bladder felt as though it did not empty at times. Residual urine amounted to 4 ounces.

A retrograde cystogram revealed an irregular bladder with a right-sided diverticulum (Fig. 25 *A*). The diverticulum re-



Fig. 25.—*A*, Retrograde cystogram in obstruction at bladder neck. Note the irregularly outlined bladder with a diverticulum. *B*, The diverticulum almost completely empties on draining the bladder.

tained a slight amount of media (Fig. 25 *B*). Fulguration of a large caruncle and dilation of the urethra with sounds failed to relieve her symptoms. After transurethral resection of the fibrotic bladder neck, residual urine was 15 cc. Her nocturia was reduced to once or twice.

*Case XIII.*—This next woman is sixty-two years of age. The history of her illness is quite protracted. Twenty-four years ago an attack of pyelitis occurred, and this was repeated fourteen and one year ago. She has never been able to complete the urinary act as fast as other people. Frequency up to every 2 hours and nocturia 3–4 times have been present for years. Residual urine up to 1000 cc. has been obtained.

Fulguration of a large urethral caruncle elsewhere two years ago failed to relieve her symptoms. Eight months after

transurethral resection of her contracted bladder neck, we find today that she has 10 cc. of residual urine and now voids quite rapidly.

*Case XIV.*—Increasing difficulty in urinating, frequency and nocturia with hematuria for six years induced this forty-three-year-old woman to enter the clinic.

Examination revealed 6 ounces of residual urine, and a contracted bladder neck with a vesical diverticulum (Fig. 26 A), which did not completely empty (Fig. 26 B). The upper urinary tract was normal. After wide transurethral resection



Fig. 26.—A, Retrograde cystogram of a small, contracted, obstructed bladder with a large diverticulum. B, The diverticulum retains most of the media because of its small orifice. The large-mouth diverticulum empties most readily, hence is less troublesome.

of her bladder neck, residual urine is 15 cc., she voids with ease, and is completely relieved.

Only the roentgenograms of the last patient are available.

*Case XV.*—When last seen in 1932 this patient was forty-one years of age. Retrograde cystogram at that time revealed a reflux of dye (grade 4) into the ureters and kidneys with extreme hydronephrosis (Fig. 27 A). Suprapubic cystotomy had been performed twice elsewhere for retention and for hemorrhage. The urine was loaded with pus and revealed *Proteus ammoniac* on culture.

This patient refused transurethral resection for her contracted bladder neck and departed wearing a cystostomy tube. Soon she removed the tube herself, the bladder closed, uremia supervened and she died after emergency nephrostomy else-

where. This is an extreme instance of kidney damage due to reflux of urine from an obstructed bladder.

*Question:* Does incontinence occur following removal of the obstructing tissue?

*Answer:* Yes, occasionally, if too much tissue is removed. Fortunately we have not seen it. Some believe the female sphincter is double. If you do not resect more than 1.5 cm. distal to the bladder neck, the sphincter should not be damaged.

*Question:* What are the microscopic findings in the tissue removed at resection?

*Answer:* Usually fibrous tissue with leukocytic infiltration and edema are observed. In four of our cases, the mucosal lining showed changes to a stratified squamous epithelium interpreted as leukoplakia. This would lend credence to the belief that long-standing inflammation in the urethra promoted the proliferative changes in the tissues, leading to obstruction.

#### DIVERTICULUM OF THE BLADDER

The relationship of obstruction at the outlet of the bladder to the formation of diverticulum is quite clear. Rarely is a congenital diverticulum seen. Diverticulum in the female occurs about thirty times less frequently than in the male because obstruction is less frequent. Prolonged obstruction with slowly developing compensatory hypertrophy of the muscle bundles of the bladder causes herniation of the bladder wall between the thickened muscle bundles by back pressure.

If the opening of the diverticulum is large, emptying occurs with urination and no treatment is necessary after the vesical neck obstruction is removed. Although some retention occurred in the instances of diverticula of the bladder presented in the illustrations above, nevertheless the urinary infections were eradicated. Surgical removal of diverticulum is rarely necessary in the female bladder.

#### STONE IN THE BLADDER

Probably less than 2 per cent of the total number of vesical calculi occur in women, because obstruction of the bladder neck is less common in women. Rarely does a large stone occur in the female bladder, hence when it does happen, errors in diagnosis are more apt to arise. Textbooks state that vesical calculi in women are most apt to form about a foreign body, either self-induced or remaining after gynecologic sur-



gery. The instances reported here were due to obstruction at the vesical neck from fibrosis in one instance and a prolapsed ureterocele in the other.

Calculus in the bladder more often fails to visualize radiographically than stone elsewhere in the urinary tract because of the larger number of urate bladder stones. Uric acid and urate stones are the most radiopermeable.

*Case XVI.*—The first patient with bladder stone, which failed to visualize, was discussed under fibrosis of the bladder neck. Her stone (ammonium urate and trace of calcium phosphate) was easily crushed with the blind lithotrite because of its moderate size (2.5 cm. in diameter), comparative softness, and the tolerance of the bladder to instrumentation.

Most of these stones in the female can be crushed with the lithotrite.

*Case XVII.*—The next woman, who is fifty-four years of age, presented the largest vesical calculus we have observed in the female. She had noticed increasing frequency of urination, both day and night, for five years. Some difficulty in urinating had been present all her life.

Examination revealed a healthy woman. The urine contained pus (grade 4) with *Escherichia coli* on culture. The cystoscope stopped at the bladder neck with a definite "clink." Vaginal palpation revealed a stony hard mass in the anterior vaginal fornix in the region of the bladder. Radiologic examination confirmed the presence of a large vesical calculus (Fig. 27 B). The kidney pelves on excretory urography were quite dilated, especially the left. Since instruments could not be introduced into the bladder, suprapubic cystotomy was performed. The stone weighed 129 gm., measured 6 by 4 by 3 cm. and was composed of calcium oxalate, calcium phosphate and urates. A large, prolapsed left ureterocele which obstructed the vesical orifice, causing retention and undoubtedly stone formation, was resected with the radio knife. The patient's convalescence was complicated by osteomyelitis of the pubic bone; this promptly healed, however, after removal of the sequestrum.

*Question:* What is the prognosis regarding recurrence of vesical stone in the female?

*Answer:* With a normally emptying bladder, the chances of recurrence are remote. Two years have elapsed now and the patient with the large stone is perfectly well.



Fig. 27.—A, Retrograde cystogram with severe obstruction of the bladder outlet showing reflux of media into both ureters and kidneys. This is an extreme example of the renal damage caused by vesical neck obstruction in the female. B, A plain roentgenogram of a large bladder stone in the female.

#### ELUSIVE (HUNNER) ULCER OF THE BLADDER

No discussion of the nature of bladder dysfunction in women would be complete without mentioning elusive ulcer or interstitial cystitis. So seldom are males afflicted with this disease that one is led to suspect as causes some changes in body economy peculiar to the female. As a matter of fact, many of these patients have had some type of pelvic surgery preceding the onset of symptoms. And most of them have had years of local bladder lavages and medication before the true nature of the disease is manifest. A better illustration of the intricacies of this lesion could hardly be found than that presented by our next patient:

*Case XVIII.*—This patient was seventy-one years of age when she first entered the clinic two years ago because of the question of tuberculosis of the kidney. For the previous ten years or more she has had frequency and nocturia up to every hour, often with extreme urgency, yet she would be unable to urinate and catheterization would reveal little urine in the bladder. Yet her bladder would feel as though it would burst, and opiates were necessary to alleviate her lower abdominal pains. Periodically she noted "plenty of pus" in

the urine when dysuria would be extreme. During these times catheterization and irrigation of the bladder relieved her somewhat. Gross hematuria had not occurred. Inventory of her general health revealed nothing of importance. She had five living children.

Examination revealed her to be quite alert for her age. Nothing unusual was found except suprapubic tenderness. Many sealed over crypts were found in the tonsils, and these were later removed. The urine contained no red blood cells and just a few white cells, but showed hemolytic *Escherichia coli* on stain and culture. The infection cleared up rapidly as the ulcers healed.

The day of admission she developed severe lower abdominal cramps and could not void; 250 cc. of clear urine with an occasional red blood cell were obtained by catheter. Later checks for residual urine were negative. Smears were negative for tubercle bacilli in the urine.

Cystoscopy under local anesthesia revealed three dull-red regions in the vertex of the bladder on the posterior wall which cracked and bled slightly when distended to 100 cc. Because

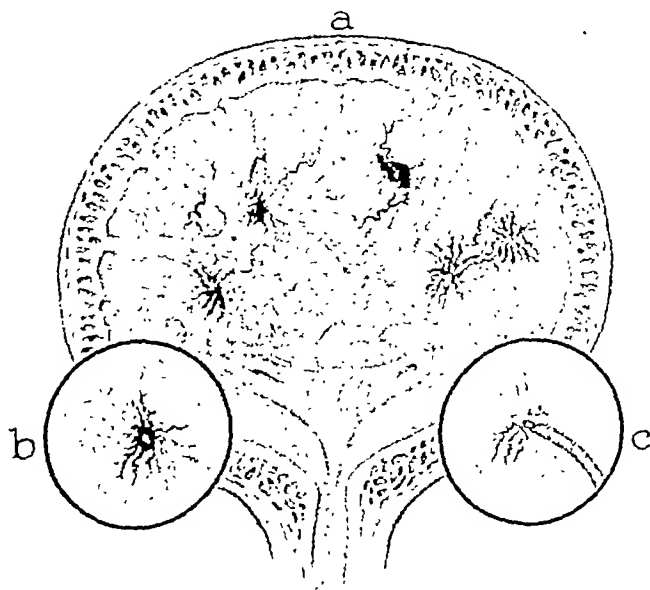


Fig. 28.—*a*, Elusive ulcers of the bladder with cracking and bleeding. *b*, Close-up of a bleeding ulcer. *c*, Electrocoagulation of a cracked, bleeding elusive ulcer.

of these patients' extreme irritability, the bladder can be properly distended to show the true nature of the ulcers only under deep general anesthesia. This was accordingly done,

with the bladder appearing normal except for the three injected regions in the vertex where the mucosa cracked when the bladder was distended to about 600 cc. Streams of blood ran from the cracks. These findings are pathognomonic of elusive ulcer (Fig. 28). The bleeding points were fulgurated lightly. Relief was dramatic. The patient felt better immediately and the next night voided only once. Within three weeks, when healing had advanced, the bladder held almost 600 cc. under local anesthesia. During the past two years she has developed periodic bladder distress, usually in the spring and fall, not unlike the rhythmic recurrence of peptic ulcer distress. At those times, thorough overdistention of the bladder to 600 cc. with possible light electrocoagulation of the ulcers provides easy and quick relief.

Although we do not know the cause of this bladder phenomenon in the female, which occurs at any age after adolescence, we must not forget that it exists and that the bladder in these women with chronic day and night frequency, after ordinary pyogenic infections are ruled out, must be overdistended under deep anesthesia in order to find these lesions. The lesions are hardly true ulcers, but when stretched are revealed as frequently bleeding cracks in the mucosa overlying a region of fibrosis involving often the entire thickness of the bladder wall and even peritoneum. The urine reveals only microscopic hematuria in many of these cases—the result of slight bleeding when the ulcers are active. Radical resection of the involved portion of the bladder rarely cures. Our best known treatment is occasional overdistention, with possible electrocoagulation of the ulcers if indicated.

#### TUMORS OF THE BLADDER

Although tumors of the bladder occur in both the male and female, it seems appropriate to include them in the group of chronic diseases often encountered in the female bladder. The most common bladder tumor is the papillary type, with *papillary carcinoma* leading by far, and the papillary epithelioma, or *papilloma*, next in order. Let it be understood that all tumors of the bladder should be regarded as *potentially malignant*.

The survival period is greatest as a rule in the case of grade 1 and grade 2 tumors, almost without regard to the current types of treatment used if proper and frequent follow-up cystoscopies are done to catch any recurrences early. We believe that tumor of the bladder is a generalized disease which is likely to spring up repeatedly in different localities of

the bladder. It is our purpose to stress favorably the *closed* or *cystoscopic method* of treating bladder tumors; this yields far more satisfactory results in the lower grade tumors and is equally as satisfactory as open surgery in dealing with higher grade lesions.

Our last patient in this series of clinics presents a valuable opportunity to evaluate the merits of open surgery against cystoscopic treatment in the presence of recurrent bladder tumor of at least fifteen years' duration:

*Case XIX.*—In 1925 this woman was thirty-two years of age. Because of hematuria she consulted her physician. (Hematuria is the leading symptom of bladder tumor.) Suprapubic cystotomy with fulguration of multiple bladder tumors was done elsewhere. Nothing further happened until 1929, when the hematuria recurred and the bladder was again opened and the tumors fulgurated by the original surgeon. The resulting hernia was repaired in 1931 and she was free of symptoms until hematuria again appeared in November, 1938, or nine years later. This time severe burning and frequency of urination also occurred.

Cystoscopy in February, 1939 revealed a large, pedunculated tumor arising near the bladder neck which waved into the urethra, producing the burning, frequency, hematuria and retention. At least a dozen other tumors were scattered about the bladder, mostly about the old operative scar and right side of the bladder. The upper urinary tract was negative. All these growths were removed transurethrally with the cutting loop or by fulguration. The microscopic report was papillary carcinoma, grade 1. In addition, the patient was given 5400 roentgens of deep x-ray therapy in twelve doses over the bladder. Repeated cystoscopic examination at two-month intervals has revealed an occasional tiny frond of tumor here and there; these are easily destroyed by electrocoagulation.

Today, eighteen months later, you see one or two tiny recurrences about pin-head size, far removed from the site of the previous lesion two months ago. I'm sure you will agree with me that from the standpoint of the patient's comfort and progress in the presence of this type of tumor, cystoscopic vigilance supplemented by roentgen therapy is far more satisfactory than fulguration in one sitting through the open bladder, such as was done twice previously in this case.

*Question:* What would be the value of segmental resection of the tumor-bearing region of the bladder in this case?

*Answer:* It would be impossible because of the far-flung positions of the tumor. The only feasible open surgery in this instance would be complete cystectomy with transplantation

of the ureters to the large bowel, not the skin, for the ureters are normal in size.

*Question:* Then cystectomy has not been advised here?

*Answer:* No, it has not. The patient agrees she would rather come in for a brief cystoscopic examination every few months now that she has survived fifteen years.

*Question:* Do these tumors change to a more malignant type in time?

*Answer:* We have no logical evidence that they do, if all sections have been taken near the base of the growth. Apparently the grade of malignancy of this tumor has not changed.

*Question:* Is radium of value in bladder tumor?

*Answer:* In this instance the recurrent tumors are too small to allow the use of radium in its most convenient form of radon seeds. These seeds are best implanted directly in the lesions cystoscopically. We have not been impressed too favorably with the use of radium in bladder tumors.



## CLINIC OF DR. IRVING F. STEIN

MICHAEL REESE HOSPITAL.

### THE MANAGEMENT OF BREECH DELIVERY AND BREECH EXTRACTION

No greater opportunity is afforded the physician to test his knowledge and skill in the art of obstetrics than in the manage-

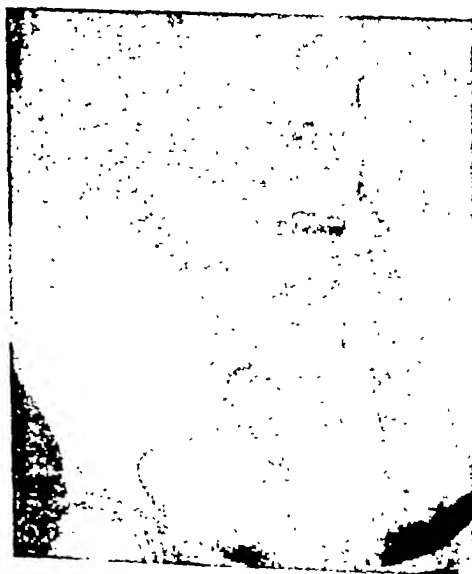


Fig. 29.—Anencephalic monster. Breech presentation.

ment of breech presentation. Although occurring in 2.5 to 3 per cent of all births at full term (more frequently in premature births), breech presentation should be considered abnormal because of a definitely higher fetal mortality and greater maternal morbidity attendant upon its treatment than occurs with occipital presentations.



Breech is a longitudinal presentation with reversed polarity, resulting from the adaptation of the fetal ovoid to the available space in the uterine cavity. Any factor which would tend to interfere with the normal cephalic lie of the fetus would contribute to its etiology. Conditions which might interfere with the engagement of the fetal head in the pelvis, such as contracted pelvis, placenta praevia and tumors of the pelvis, are not infrequently associated with breech presentation;



Fig. 30.—Twin pregnancy. Cephalic and frank breech presentation.

multiparae more than primiparae (by 3 to 2), and multiple pregnancy, hydramnion and fetal malformations such as anencephaly (Fig. 29) and hydrocephalus, often present as breech. Before term the fetus enjoys greater mobility in the uterus and there is relatively more liquor, hence breech presentation is more frequent in premature births. In twin pregnancy 34.2 per cent of presentations occur as breech and cephalic; 8.4 per cent as breech for both fetuses and 3.6 per cent as breech and transverse (Fig. 30).

## DIAGNOSIS

A full appreciation of the above factors is requisite to the intelligent management of breech delivery, and a thorough examination must be made in order that a correct and complete diagnosis be reached. Of great aid in clarifying these factors, and one not sufficiently emphasized in obstetric textbooks, is the *radiologic study* of the pregnant women at or near term.



Fig. 31.—Complete breech presentation. Full term.

Roentgenograms reveal,<sup>1</sup> more vividly and more accurately than any other method of examination, the bony development, approximate size and especially the *attitude* of the fetus in utero. The shape and size of the pelvis are shown as well as the fetal-pelvic relationship. With the use of x-rays the physician may determine accurately whether he is dealing with complete breech or frank breech presentation.

*Complete* breech is a presentation in which the extremities are well flexed, with the feet against the buttocks, the arms folded on the chest, the spine bent in C formation, and the head bent forward. In other words, the fetus is in an attitude of complete flexion (Fig. 31). The *incomplete* or *frank* breech presentation (Fig. 32) is one in which the legs are extended along the fetal trunk, with the feet often found up under the

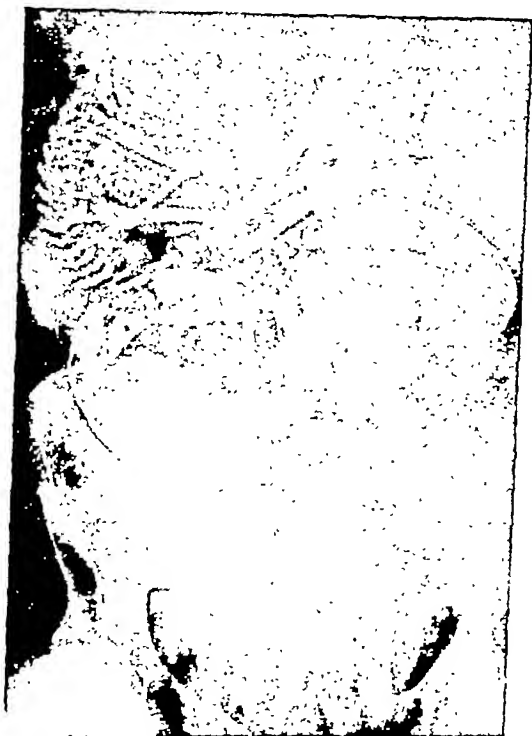


Fig. 32.—Twin pregnancy. Incomplete or frank breech presentation of first fetus.

chin; one or both legs may be prolapsed or one or both knees may present in the vagina. The spine is straight and the head is held erect as in the military attitude. Sometimes the head is turned towards one shoulder, or is thrown back, comparable to brow in cephalic presentation (Fig. 33). The arms also may be found away from the chest, extended over the head or down along the trunk, or may be otherwise displaced,

These factors usually elude ordinary methods of clinical

examination, but may be discovered by the x-ray. One must be cautious, however, in interpreting the findings in the fetal roentgenogram. Mistakes are frequently made due to distortion of fetal shadows. Fetal death may be erroneously diagnosed<sup>2</sup> due to angulation of the spine or apparent overlapping of the head bones (pseudo-overlapping). If the head lies anteriorly in the fundus, a film taken with the woman in dorsal posture may show a magnified head shadow simulating hydrocephalus (Fig. 34). Such a diagnosis has been made when

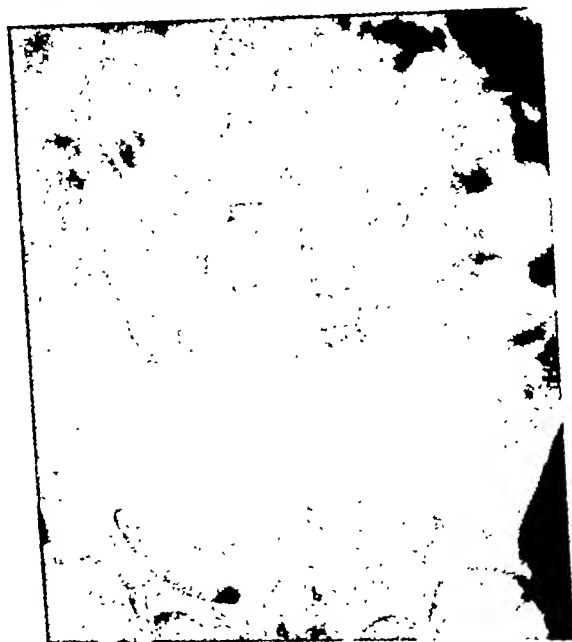


Fig. 33.—Extreme deflexion attitude of breech simulating (inverted) brow presentation.

subsequently a normal child was delivered. One should not rely upon a single film, but should study prone and lateral views. In this way errors can be obviated.

The diagnosis of breech presentation ordinarily is not difficult, and can frequently be made by careful palpation of the abdomen. The presence of hydramnion, however, or of multiple pregnancy, an irritable uterus or rigid abdomen may complicate the picture and render the diagnosis difficult. It is especially in such conditions that the roentgenograms are useful.

In breech presentation the buttocks present, and the sacrum is designated as the *point of direction*. Breech usually occupies the right oblique portion of the pelvis, in the position of sacro-left-anterior or sacro-right-posterior.

*External examination*, made in the usual orderly sequence of Leopold's four procedures, reveals that the fetal ovoid is longitudinal; a firm, round and ballotable body, the head, is in the fundus and this is the chief determining factor in the diagnosis. The smooth back is found on one side, with a cleft

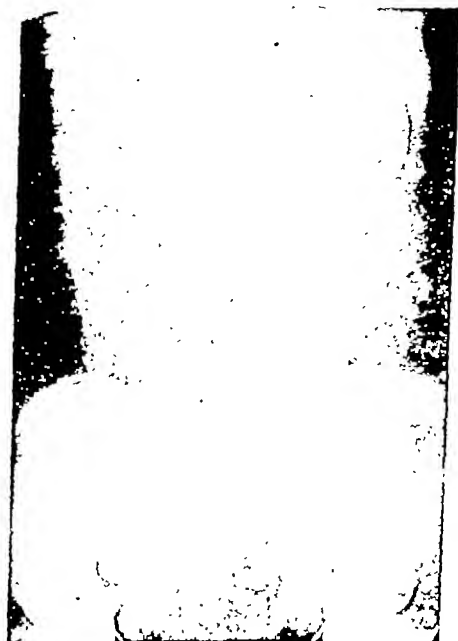


Fig. 34.—Normal fetus, breech presentation. Dorsal posture. Mistaken for hydrocephalus because of distortion of head shadow.

between the head and fetal back; and the heart tones are best heard over the back, usually above or at the level of the umbilicus. The extremities are palpable on the side opposite the back in the fetal triangle. Above the pubes one feels the continuation of the fetal back terminating in an irregular body which lacks the hardness and the smooth contour of the head.

*Rectal or vaginal examination* often reveals the pelvis to be empty unless the patient is well advanced in labor, as the breech usually engages late. After the cervix has become

effaced and dilated, the irregular soft buttocks, the tuberosities, the genital crease (or scrotum) and the tip of the sacrum can be identified by the examining finger. One can differentiate the breech from face presentation, with which it is sometimes confused, by inserting a finger into the anus after rupture of the membranes. If the fetus is in an attitude of complete flexion, one or both feet may be palpated along the buttocks. The appearance of meconium is usual after the membranes have ruptured, and does not portend asphyxia of the fetus as it often does in cephalic presentation.

#### THE COURSE OF LABOR IN BREECH PRESENTATION

The course of breech labor is usually longer than labor with cephalic presentations. The breech remains high until near the end of the first stage of labor, and premature rupture of the membranes is a common occurrence. Obviously there is danger of prolapse of the cord, or of one or both feet. The buttocks are at best a poor dilator for the cervix, and particularly in primiparae is the dilatation apt to be slow. Later the cord may suffer compression at the pelvic brim when the trunk is born and the shoulders and head remain to be delivered.

The position of the fetus in the incomplete variety of breech is quite similar to the deflexion attitudes in cephalic presentation, and, as in the latter, the fetus travels a more difficult course through the birth canal. The amount of alteration of the mechanism of labor depends somewhat upon the degree of deflexion of the fetus. The extended thighs act as splints for the trunk, thus preventing lateroflexion in the birth canal and frequently demanding extraction of the fetus. Extended arms which may lie in a nuchial position owing to traction on the legs and trunk before full dilatation of the cervix, or to pressure on the fundus before the shoulders engage in the pelvis, may tax the ingenuity of the obstetrician to dislodge them without injury. The deflexed head may also be arrested above the pelvic inlet and, unless maneuvered correctly and in time, may be the cause of fetal asphyxia or serious intracranial injury. Extraction may be extremely difficult under these conditions—a factor contributing materially to fetal mortality and morbidity. In breech cases the fetal head may be round, or more often, dolichocephalic; because there is no molding during the first stage of labor, the head offers considerable resistance to engagement and to extraction. Whether the head is primarily dolichocephalic and

thus a cause of the presentation, or whether it becomes so because of pressure against the uterine fundus, is of but academic interest.

The *size* of the fetus and of the pelvis are also factors determining the course of labor. Small and premature babies rarely present delivery difficulties unless traction is made before complete cervical dilatation. A moderately contracted pelvis, however, and especially a contracted outlet, may cause serious obstacles to delivery.

#### TREATMENT

**External Version.**—Some obstetricians advocate external version in breech cases during late pregnancy or in the first stage of labor, but I do not subscribe to this practice. Recently, however, I had occasion to make exception to this rule when a patient seven months pregnant consulted me because a physician had advised her that cesarean section would be necessary because of the breech presentation. While explaining that the fetus often changes its position even late in pregnancy or in the first stage of labor, I very easily performed external version. I then instructed her to return to her physician and request re-examination and a reconsideration of his plan for delivery. The patient had lost confidence in the doctor who had alarmed her unnecessarily, and dismissed him from the case. Her delivery was spontaneous, with the fetal head in the left occipito-anterior position. This case illustrates that in some instances external version can be easily accomplished. However, most frequently the fetus returns to its original position. Furthermore, cord complications, premature rupture of membranes, and placental separation may result from the manipulation. If all cases of breech were converted into cephalic presentations, and if they remained so, we would lose good teaching material at the risk of meddling manipulation. If the fetus has adapted itself more comfortably in the uterine cavity in this position, deliver it as such but first ascertain all of the available facts which will contribute to the safe conduct of the case. The size and number of fetuses, the shape and condition of the uterus, the character of the contractions, location of the placenta (whether placenta praevia), and the state of the cervix and membranes, should be known before delivery. Physical and roentgenographic examinations will furnish valuable data of diagnostic import. I wish to reiterate that one must be capable of interpreting the x-ray findings in order to avoid grave errors.

**Conduct of the First Stage of Labor.**—Breech should be treated with prepared expectancy. Everything should be in readiness for a sudden delivery or extraction: anesthesia, local or general, the proper table, light, assistance, and forceps for the after-coming head. Forceps and all other materials for delivery and for treating asphyxia must be sterilized well in advance, as they may have to be used at a moment's notice. A policy of noninterference should be adopted during the first stage of labor, there being no need for vaginal, and little excuse for rectal examination once the diagnosis has been made. Progress can be noted by the nature of the pains and by external examination alone. Location of the heart tones is of value, and a frequent check should be made throughout labor. When the membranes rupture a new diagnosis must be made, taking into account the state of the cervix, the umbilical cord, the extremities, whether the breech has engaged, the position, and whether it is the frank or the complete variety. Before the second stage begins, the delivery room should be set up, the anesthetist should be present, and the patient is draped for delivery. Still there should be no active intervention unless indicated by the condition of the mother or the baby. Fetal heart tones should be recorded frequently.

**Breech Delivery vs. Breech Extraction.**—The decision to deliver or extract the fetus is made with much the same reasoning as concerns forceps extraction in head-first deliveries. If progress is satisfactory, and no indication of danger or need for haste arises, breech delivery is indicated. Contrarily, if the heart tones are irregular or weak, or if the mother suffers hemorrhage, or, in the case of frank breech, midplane arrest may demand breech extraction. The difference between breech delivery and breech extraction is that in the former the patient delivers herself until the region of the umbilicus is born, when manual aid for the arms and head is given. In breech extraction we have a condition similar to forceps extraction in cephalic presentation, except that we do not use forceps on the breech.

**Technic of Breech Extraction.**—In former days forceps, fillets and hooks were used to extract the breech. However, today the child is extracted from the birth canal by one of the following methods: (1) In *complete* breech, if one or both feet are accessible in the cervix or vagina, they are grasped and drawn down; traction on the legs causes the buttocks, back, shoulders, arms and head to be successively born. (2) If the legs are extended, as in *frank* breech, a finger in the



anterior groin, assisted by one posteriorly when the posterior buttock appears, is used for traction in the direction of the birth canal. Considerable force is often required for this type of extraction. (3) When the breech is *high*, or is readily decomposed, it is better to bring down one or both legs. This may be accomplished by first dislodging the breech and then tapping the popliteal space to cause flexion of the leg and render the ankle accessible to the operator's hand. *Pinard's maneuver* may be similarly used: the thigh is abducted with the finger, causing the leg to flex; the ankle can then be grasped and the leg brought down. When one or both feet are out, and the knees are at the vulva, the hips are then engaged in the inlet. The heart tones should be checked. As the buttocks descend, rotation should be made so that the feet appear toes up. The breech then sits on the pelvic floor. In this way the fetus is flexed in the pelvis and, according to Potter, passes along the axis of the birth canal most logically.

*Delivery of the Trunk and Arms.*—Potter also suggested many of the following steps, which appear most reasonable, for delivery of the trunk, arms and head: Hold the feet of the child and twist the one to become anterior upward, while the other foot is carried backward to bring one hip under the pubes. When the trochanter stems under the symphysis, upward traction on both legs will permit the posterior hip to appear over the perineum. Preliminary ironing out of the vagina and perineal body sufficient to admit the operator's fist is a wise preparatory procedure in breech cases. In primiparae, an additional episiotomy made just as the buttocks distend the vulva will serve to facilitate the delivery of the head, and may prevent a third degree perineal laceration which so often results from unskilful management. Further traction on the legs and trunk, with the thumbs parallel to the fetal spine (the fetus covered with a warm dry towel), will bring the anterior shoulder under the symphysis. Meanwhile, a loop of cord is drawn out, and the pulsations constantly noted. Now, instead of the Müller maneuver of alternately pulling strongly downward and then upward on the trunk to stem the shoulder, the fetus is drawn downwards, and a finger in the anterior axilla exerts backward pressure on the scapula. This causes the anterior arm to flex on the chest and to drop into view for easy delivery. The fetus is then rotated posteriorly so that the other shoulder comes to lie anteriorly under the pubis; the other arm is similarly delivered.

*Delivery of the After-coming Head.*—Now we are ready

for the final and most precarious, as well as the most important step, namely, the delivery of the after-coming head. The first principle to be observed is that *flexion* is of paramount importance. Second, the head should be delivered in an occipito-anterior position if possible. Accordingly, when the arms are outside the vulva, the child's trunk is made to rest astride the operator's left forearm, while the index finger of the same hand seeks the fetal mouth. With a finger in the baby's mouth, just enough traction is made to flex the head, care being taken to avoid injury to the articulations of the jaw and to the soft parts. After flexion has occurred, the head is led down in one of the oblique diameters of the inlet, aided by gentle but firm external pressure with the right hand over the pubis. This is the only time pressure from without is exerted upon the uterine fundus, for if fundal pressure is made before the arms engage in the pelvis, the head descends and the arms are apt to extend up over the head. Now, either the time-honored *M.S.V.* (named successively for the great obstetricians Moriceau, Smellie, and Veit) or the *Wiegand-Martin method* should be tried; but if the head does not readily yield to these manual methods of extraction, then forceps on the after-coming head should be used.

The *M.S.V.* requires that the fetus, riding on the left forearm of the operator, head well flexed by means of the index finger in the fetal mouth, is grasped for traction by the operator's right hand. The fingers are spread over the fetal neck so that the tips rest *on the clavicles* or sternum. Here traction can be made with the greatest safety. One should particularly avoid compression of the fetal neck. While strong traction downward is now made with the right hand, the left maintains constant flexion of the head and also raises the body up to the vertical. In this way the mouth soon appears at the vulva where it can be freed of mucus, and the child can breathe if need be. The chin, nose, eyes, forehead and entire head successively follow over the perineum.

The alternate procedure, and one favored by Potter, who has had a vast experience with version and extraction, is the *Wiegand-Martin method*. In this the head is flexed as before, the face turned to one side so that the head enters in the transverse diameter of the inlet; instead of traction with the right hand, pressure is made upon the head from without. The flat hand is laid over the pubis, and strong downward pressure is made directly over the head to cause it to enter the pelvis. When the head has engaged, the legs are grasped and drawn

upwards over the maternal abdomen as the head descends and finally emerges through the vulva.

Whenever either of these manual aids proves to be too difficult or seems to require too great a force on the delicate fetal parts, the decision should be promptly made to extract the head with *forceps*. Inasmuch as about eight minutes is the limit of safety from the time the umbilicus is born until the delivery of the head, all decisions concerning the method of extraction must be made with dispatch, and all instruments must be in readiness for instant use.

While any good obstetrical forceps can be used for delivery of the after-coming head, I recommend the Piper instrument most highly. This blade is especially designed for easy and safe extraction (Fig. 35). The long shank makes the instrument springy, and the perineal curve facilitates han-

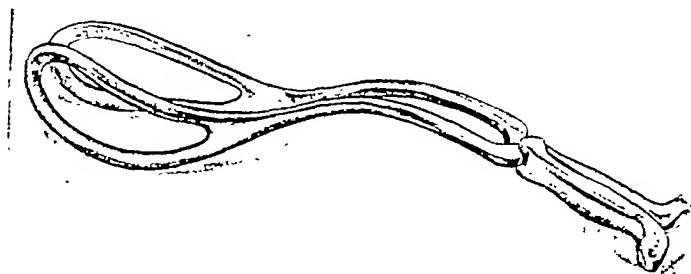


Fig. 35.—Piper's forceps for extracting after-coming head.

dling it in the presence of the exposed fetal trunk. An assistant holds the child upward, and the blades are inserted as with any other forceps, the left or lower blade first, directly to the sides of the child's head. Horizontal traction will increase flexion of the head and extract it without difficulty. I have found the Piper forceps to be an invaluable aid in the management of breech.

Should the head come down as occipito-posterior, one carries out the same procedures except that the M.S.V. is *reversed*, i.e., the posterior hand makes traction upward, while the anterior hand maintains flexion of the head by means of a finger in the mouth. Rotation of the head to anterior sometimes can be accomplished after grasping the fetus for extraction.

The *reversed Prague maneuver* may also be tried. In this, the shoulders are grasped from behind with the left hand, the

fetal back riding the operator's forearm, while the feet are carried strongly upward by the operator's right hand. These methods failing, the Piper forceps may be used in the same manner as with occipito-anterior position, the fetal body being held well anterior while placing the blades.

*Displacement of the Arms.*—When the arms become displaced over the head or in a nuchal position, the obstetrician finds himself in a delicate predicament. There is great danger of fracture of the arms and clavicles, and risk to the life of the fetus due to the additional time consumed in attempting to rectify the error. Never try to deliver the head until the arms are free, and until they lie outside of the vulva. There is not room in an ordinary normal pelvis for the passage of a head and an arm together. Furthermore, breech often occurs because the pelvis is smaller than normal, and the resistance offered by the bony pelvis may cause displacement of the arms. Therefore, before strong traction is made to deliver the shoulders, be reasonably sure that the arms are flexed. Proper conduct of the case will prevent displacement of the arms.

If one arm is extended *over the head*, the trunk should be pushed slightly upward in the birth canal and the displaced arm rotated posteriorly. The hand of the operator, with the palmar surface facing the fetal back, should be introduced along the back to the arm, and along the humerus until the elbow is reached. Then, and not until then, should effort be made to bring down the arm. Traction on the humerus almost invariably results in fracture! The elbow, or better still, the forearm, should be carried forward across the face to the chest, where it can easily be delivered by straightening out the arm.

If the arm assumes a *nuchal* position, it is imperative that it be released before attempting delivery of the head. First determine which arm is in the nuchal position. Then insert the corresponding hand along the fetal back so that the fingers can grasp the elbow. With the other hand, rotate the fetal trunk in the opposite direction, so that the forearm can slip past the head and come to lie in front of the chest. This procedure may prove to be both difficult and time-consuming, especially with a large baby or in the presence of a contracted pelvis. As soon as the child is born, the air passages should be cleared by aspiration. A tracheal catheter is kept in readiness for the administration of artificial respiration.

*Death of Infant During Delivery.*—In some cases the fetus dies during delivery, and the physician may encounter great difficulty in delivering the head. Whether the obstacle

is a contracted pelvis, a large head, a deflexed head, or an abnormal one such as hydrocephalus, once the baby is dead one should have no hesitancy in performing a craniotomy. Palpation of the cord or palpation directly over the precordium will verify the condition. Forceps should not be used in such cases, as there is greater risk of injuring the mother with them than with craniotomy. Craniotomy can be accomplished easily by making downward traction on the fetal trunk using the body as a handle, steadying the head from above, and perforating the fetal skull by Naegele's technic. This may be done through the foramen magnum, through the occipital bone, through the roof of the mouth, or one orbit, according to the accessibility of the parts. After perforation, the brain and cerebral fluid are drained out and the basiotribe applied. Extraction of the crushed head is completed without difficulty as a rule. Care must be taken that sharp spicules of bone do not injure the maternal soft parts.

**Cesarean Section.**—The question is often asked whether cesarean section is not justifiable in cases of breech. The answer is that when the pelvis is normal and the fetus proportionate in size, unless there exists some complication demanding prompt uterine evacuation, there is no indication for a cesarean operation. However, when the pelvis is contracted or the fetus is oversized, or when a placenta praevia or tumor of the true pelvis, a fulminating and uncontrolled toxemia, or other accepted reason for hysterotomy is present, then section should be done. Age alone is not a valid reason, as we have delivered babies presenting as breech in primiparae near the forty-year age without unusual difficulty.

#### PROGNOSIS

While the mortality is usually not increased in breech cases, maternal morbidity is indeed greater than with cephalic presentations. *Lacerations* are more frequent, and third degree tears too often occur from too rapid delivery of the after-coming head. *Hemorrhage* and *sepsis* may result from the increased vaginal manipulations. *Placenta praevia* frequently is associated with breech, and *premature separation* may occur during delivery. Both of these complications may be the source of jeopardy for the mother by demanding haste in delivery of the child.

The fetus is in grave danger of asphyxia, only about eight minutes being allowed after the umbilicus appears for delivery of the head. Haste may produce arm complications resulting

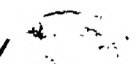
in fractures and increased difficulty in extraction. Whenever extraction is attempted before complete cervical dilatation, there is danger of arm displacement and of retraction of the cervix about the neck of the child. Further traction may result in deep lacerations, uterine prolapse, and postpartum hemorrhage.

#### SUMMARY

1. Diagnose breech presentation by clinical means, and study roentgenograms for detailed knowledge of the condition.
2. Be prepared. Know whether there is a single fetus, normal or monstrous, twin or triplet, and the complications.
3. Do not correct by external version without good cause. Gain experience in managing breech delivery.
4. Know the difference between breech delivery and breech extraction.
5. Treat by prepared expectancy, whenever possible. Do not deliver by cesarean section unless it is really indicated.
6. Have an adequate forceps ready for the after-coming head if manual aid methods fail.
7. Be prepared to treat fetal asphyxia.
8. There should be no more maternal mortality than with cephalic deliveries, and the fetal mortality and morbidity will be proportionately lowered as the physician grows in experience.

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## CLINIC OF DR. J. ROSCOE MILLER

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#### DIAGNOSIS AND TREATMENT OF FEVERS OF OBSCURE ORIGIN

DURING the past century the attitude toward fever has undergone considerable change. In the textbook of an earlier period one will find fever discussed much as specific diseases are considered today. Fever was divided into numerous classifications and treatment prescribed for each. We no longer look upon this phenomenon in such a manner but rather view variations in temperature as but an expression of the body's reaction to disease.

The heat-controlling centers are located at or near the hypothalamus. Injury to this section abolishes the ability of the experimental animal to adjust its body temperature when exposed to cold.<sup>1</sup> The center for heat dissipation is located in the upper part of the midbrain and extends upward into the hypothalamus.

In maintaining an even temperature there must be a balance between the heat produced by the tissues and that dissipated by the body. *Factors in heat dissipation* may be listed as follows<sup>2</sup>:

1. Radiation, convection and conduction.
2. Evaporation of water from the lungs and skin.
3. Raising inspired air to body temperature.
4. Liberation of carbon dioxide from the blood in the lungs.
5. Loss of heat in urine and feces.

The first two normally account for over 90 per cent of the heat lost. It is well to keep these various factors in mind when discussing fever, since interference with normal functioning will result in temperature changes.

As Blumer<sup>3</sup> has pointed out, there are seventy-five febrile diseases of specific etiology listed in the textbooks, to say nothing of the many from noninfectious causes. In considering a given case which presents fever only, we can eliminate imme-



diately many causes of fever which give other manifestations as well, and which are usually recognized without difficulty. Thus we can readily rule out acute exanthemata and febrile infections such as tonsillitis, wound infections and other conditions typified by other characteristic findings.

When attempting a diagnosis in a febrile case with few or no signs, two things should be kept in mind: (1) it may be an atypical example of a common disease or (2) it may be a relatively common disease but one not seen frequently in this particular locality. To cite an instance of the first, postnasal infections are commonly the cause of fever but may present few or no symptoms, while in the second category might be mentioned malaria, which in many localities is always considered as a first possibility, while in others it is farther down the list since it is seen but seldom.

It is needless to call attention to the importance of a careful *history* as the first step in arriving at a conclusion.

Since there are so many pathologic conditions typified by fever it is necessary to adopt some sort of *classification* to simplify differential diagnosis and so that no cause of pyrexia will be inadvertently omitted. Keefer<sup>4</sup> in addition to a miscellaneous group divided his cases into (1) specific infections, (2) tumors, (3) disorders of blood-forming organs, and (4) disorders of the heat-regulatory mechanism. This is a good working classification and to it should be added (5) fever of dehydration, (6) fever produced by drugs, (7) surgical fever arising from extensive aseptic surgical procedures and probably on a toxic basis, (8) miscellaneous fevers, where the cause is obscure but is probably to be found in one of the specific classifications.

#### OBSCURE FEVERS IN SPECIFIC INFECTIONS

This group is, of course, the most common. It contains all the acute and chronic infections. To rule each one out separately would take considerable time and fortunately is usually unnecessary. There are, however, a number of conditions which fail to give typical signs and symptoms, and it is to these that our attention should be turned.

**Postnasal Infection.**—O'Connor<sup>5</sup> has called our attention to the fact that one of the most common causes of continued low grade fever is to be found in a postnasal infection. The first case is a good example of this:

*Case I.*—The patient is a woman aged twenty-seven years. Her presenting complaints were loss of five pounds in weight, fatigue, chest pain and a low

grade fever. These had been present for about three weeks prior to examination. Inventory by systems and past history were irrelevant. The findings upon examination were essentially negative except for a fever of 99.8° F. and a diffusely injected nasopharynx. The tonsils had been removed. The white blood count was 6500, red corpuscles 4,500,000, hemoglobin 13.3 gm. The differential count was within normal limits. x-Ray examination of the lungs revealed no pathology. Urinalysis was negative. A culture taken from the throat gave an almost pure growth of *Streptococcus viridans*. The patient was treated by an otolaryngologist, with early improvement and disappearance of symptoms within a week. She returned six months later with similar complaints and findings and again responded promptly to treatment. There have been four recurrences at intervals of six to ten months, always of short duration after therapy was instituted.

**Prostatic Infection.**—Another focus of hidden infection frequently overlooked is the prostate. The following case is an example of sepsis arriving from that source.

*Case II.*—The patient, aged forty-six, suffered from an acute upper respiratory infection in January. This lasted for ten days and gradually the symptoms disappeared. However the patient continued to feel debilitated and decided that a winter holiday would hasten recovery. He consequently spent the month of February in Florida, returning somewhat improved but still not feeling as well as prior to his respiratory infection. He was seen soon after his return. At this time he had no specific symptoms referable to any particular system. His previous weight of 156 pounds had fallen to 146 pounds. His appetite was poor and he suffered from headaches and insomnia. History prior to January 1 was irrelevant. Examination revealed no evidence of infection in the head and neck. The tonsils had been removed. Sinuses were clear. The lungs were negative to x-ray and physical examination. The heart rate was consistently between 90 and 100. There were no other noteworthy cardiac findings. The abdomen and extremities were not remarkable. Significant laboratory findings included an elevated white cell count (14,000) and a mild hypochromic anemia. Serology and agglutination tests were negative. A tuberculin test was negative. A two-hour temperature record followed for one week showed elevations of 1° to 2° F. every afternoon.

Despite absence of symptoms referable to the genito-urinary tract the patient was sent to a urologist who massaged the prostate and examined the secretions. The first examination was negative but on examination five days later a dram of pus was expressed. Massage twice each week, together with chemotherapy, was followed by complete recovery. Within a month the patient had gained 12 pounds in weight, his temperature remained normal and the white count dropped to 8500. He has had no recurrence in the intervening five months.

**Tuberculosis.**—Whenever a patient is found to have a continued temperature without explanation, tuberculosis is rightly considered early in the differential diagnosis. As a rule, careful examination aided by laboratory procedures such as the x-ray and the sputum test will serve to establish or rule

out a diagnosis of *pulmonary* tuberculosis. Examination of stomach contents obtained by lavage will often reveal the tubercle bacilli in cases where there is no cough and therefore no sputum for examination. However the search should not stop here. Madding and Masson,<sup>6</sup> in reporting tuberculosis of the *retroperitoneal lymph nodes*, point out that approximately 10 per cent of primary tuberculosis is found below the diaphragm. In the adult, tuberculosis of the *intestine* is usually secondary to pulmonary involvement and marks the widespread dissemination of the original infection. In children, however, this is not the rule, a primary infection being not uncommon. This is usually the result of invasion of the bovine type and the most common site of involvement is the *cecum*. Healing may take place but the process is of long standing and in the less severe cases a prolonged low grade fever with gradual emaciation results. Hyperplasia often produces palpable tumor masses in the right lower quadrant and multiple constrictions are common. When this stage is reached x-ray examination will be of aid but it is earlier that a diagnostic problem is presented. As an aid to early diagnosis the use of the tuberculin test and x-ray examination are important. If the process is active, the tubercle bacillus can be isolated from the stool. Treatment follows that indicated in tuberculosis elsewhere: prolonged rest and supportive measures with special attention to nutrition.

**Undulant Fever.**—In the past decade we have become increasingly aware of the prevalence of undulant fever, and it must always be considered in a febrile patient without noteworthy signs. By far the largest number of infections result from ingestion of infected milk; however, other means of infection exist. The disease can result from contact through abraded skin, meat handlers in particular being affected in this way. Flies may serve as carriers. Thus it is seen that undulant fever cannot be safely excluded as a possibility even in those who use pasteurized milk exclusively, although it is much less likely to occur in those using a safe milk supply.

A characteristic fever has resulted in giving the disease its popular name, although not all cases exhibit this type of abnormal temperature. Because it can exist without characteristic signs the disease should be given early consideration in cryptogenic pyrexia; in fact, symptomless infections make up the largest number of cases, the organism being present for long periods of time without seriously affecting health. The lowering of resistance from some other cause may be followed

by a prolonged illness, with bouts of fever. As a rule the only symptoms are lassitude, weakness and headache, accompanied by a low grade fever.

As is usual in conditions with slight elevations of temperature, anorexia develops and as a result the patient loses weight. At this point tuberculosis is suggested, particularly since in both conditions slight hemorrhage from the bowel may appear. Few signs aid the diagnostician although a number are occasionally seen. Perhaps half the cases exhibit a splenomegaly, and an early macular skin eruption occurs but is often overlooked. The patients do not generally appear to be seriously ill.

*Special diagnostic procedures* include the agglutination test for brucellae in the blood, the skin test, the opsonocytophagic index, and blood and urine cultures. The organism may be recovered from the stool. Although requiring considerable time, guinea-pig inoculation with 2 cc. of whole blood is a reliable procedure. Fortunately the disease runs a definite course of three to four months' duration. The mortality rate varies but is usually about 3 per cent. No definite cure is known at this time. Supportive treatment is important. An antiserum is available and good results have been reported with chemotherapy.

**Typhoid Fever.**—Typhoid fever, once among the most common diseases in the United States, has so decreased in frequency that it is now rare in many localities. In three decades between 1900 and 1930, the incidence in this country dropped from 6 per 1000 to 0.2 per 1000 and it is now generally recognized as an index of the sanitation and health standards of a community. Because it is now uncommon, however, it may be overlooked as a cause of long continued fever. A well developed case offers little difficulty in diagnosis, but it is sometimes necessary to resort to laboratory methods in the mild and atypical cases. The agglutination reaction (Widal) becomes positive during the second week and is a valuable aid in diagnosing an unusual case.

**Tularemia.**—This is another condition which deserves special attention, since we now know it to be widespread and relatively common. The usual case with abrupt onset, chills, high fever and prostration does not present the problem offered by the mild, ambulatory case which is not a rarity. The fever curve may be marked by remissions. As a rule the onset is presaged by the appearance of an ulcer which is followed by lymphatic enlargement; however, it should be remembered

that the causative organism may enter through the unbroken skin and cause no ulcer. An investigation of any obscure fever should include an agglutination test for *Pasteurella tularensis*, which becomes positive during the second week and sometimes persists for years.

Treatment is largely symptomatic, although the intravenous injection of serum has resulted in a lowered mortality rate and shortening of symptoms.

**Relapsing Fever.**—Although little attention is usually given to relapsing fever, this condition should be considered in obstinate fevers occurring in certain localities. The disease is due to a variety of a spirochete known as *Borrelia*. In this country it is transmitted by ticks, actual infection resulting from the introduction of the feces of the tick into skin abrasions. It is characterized by sudden onset, generalized aches and pains, and a fever which may rise to 103° F. or more. After several days the fever subsides, to reappear after two weeks. During the febrile attacks the liver and spleen enlarge and the causative spirochete may be found in the blood smear. The disease is self-limited and arsphenamine is curative.

**Rickettsial Infections.**—The rickettsial infections, particularly *typhus fever*, will undoubtedly require our attention to an increasing degree in the future. Typhus fever is not a rare condition at the present time although usually seen in vagrants and those living under insanitary conditions. However, since it is a louse-borne disease it accompanies any catastrophe which affects sanitation and encourages crowding. War is perhaps the foremost factor in producing unusual insanitary conditions. The present conflict in Europe will undoubtedly be followed by widespread epidemics, particularly since large numbers of refugees are wandering from country to country, crowded together without any semblance of hygiene. Poland in particular has been so affected and since it has always been regarded as a reservoir of typhus fever it seems probable that in this as in previous conflicts the toll of human lives will be as great from the bite of the louse as from implements of war.

The louse is no respecter of person and would as soon bite prince as pauper, so that typhus may be found in any walk of life. Its distinguishing feature is a *skin eruption*, appearing in a single crop, first macular and finally petechial in character. It is generalized except for the face. Unfortunately this rash is variable in severity and may not appear for seven to ten days after onset, thus leaving the diagnosis obscure in some

patients. Of valuable assistance in making a diagnosis is the Weil-Felix agglutination test which is positive in practically all cases.

There is no specific for the disease, treatment being symptomatic. Careful nursing care seems to be of unusual importance.

*Rocky Mountain spotted fever* is another rickettsial infection, clinically almost indistinguishable from typhus. It has a wide distribution in this country and is transmitted from animals to man by ticks. Treatment is again symptomatic.

**Rheumatic Fever.**—Malaise, generalized fleeting pains, anorexia and pyrexia occurring over a period of weeks, particularly in children or young adults, should always lead to the suspicion of rheumatic fever. It should be remembered that in youth rheumatic fever need not produce a polyarthritis and that the prodromal symptoms are often prolonged for a period of weeks or months. Since there is no specific diagnostic test, careful observation with special attention to each new complaint or sign is important. Where arthritic manifestations are present, little difficulty is encountered; however, their absence should not be taken as reliable evidence that the condition does not exist. The presence of chorea, of subcutaneous nodules, and of heart findings particularly where the sedimentation rate is much increased and the auriculoventricular conduction time is variable in the electrocardiogram should lead to the correct diagnosis.

Treatment is largely supportive. The salicylates relieve pain, and bed rest is absolutely essential. It is better to err by keeping the patient in bed an extra week than to allow activity too early. Even after complete subsidence of fever the variability of the systolic murmur which may be an important sign, and the A-V conduction time as measured by the electrocardiogram and the pulse rate serve as valuable guides in deciding upon the date of commencing activity. Exercises, when begun, should be graduated.

**Subacute Endocarditis.**—Whenever recovery from an acute infection is slow and marked by continued low grade fever, an endocarditis should be suspected. Acute endocarditis usually develops in such a manner as to remove doubt at once of its identity, but subacute bacterial endocarditis is frequently undetected in its early course. While not rare it is fortunately not a common complication. It is nearly always seen in individuals who have suffered previous endocardial damage, although sometimes this previous insult has gone unrecognized,

the victim and even the doctor not suspecting the underlying pathology.

The usual history is that of an acute upper respiratory infection from which the patient fails to recover, symptoms of malaise, debility and prolonged low grade fever indicating a hidden focus of infection. Examination at this time will probably reveal signs of the pre-existing cardiac pathology. These include mitral stenosis with eccentric contour, presystolic murmur and thrill, although the valve may not have suffered sufficient damage to result in these. Occasionally there may merely be an apical systolic murmur. Gradually other evidences of systemic infection appear. Careful search will eventually be rewarded by the discovery of petechiae, which appear earliest and most often in the retina, conjunctiva and nail beds. Since the kidneys possess a relatively massive network of blood vessels it is little wonder that emboli find lodgment there, and a careful microscopic urinalysis will show varying amounts of red blood corpuscles. Splenomegaly is the rule, and finally a blood culture will show the presence of the *Streptococcus viridans*. It is never amiss to mention the necessity for care in making these cultures and the fallacy of relying on one or two negative tests. The disease is usually fatal. Chemotherapy has been reported as curative in a few cases.

**Infectious Mononucleosis.**—Infectious mononucleosis or glandular fever is an acute infectious disease characterized by fever. In addition there is a marked enlargement of the palpable lymph nodes throughout the body, which appears about the time the fever reaches its height. These glands are soft and slightly tender. Other characteristic symptoms include conjunctivitis, malaise, pharyngitis and epistaxis. The blood picture is unique, a slight polymorphonuclear rise being followed by a neutropenia and a mononucleosis which may reach as much as 99 per cent. Davidsohn's modification of the Paul-Bunnell test is an aid in diagnosis. The disease is self-limited and treatment is symptomatic.

**Intestinal Parasites.**—Intestinal parasites are always to be considered in undiagnosed pyrexia and during stool examinations a careful search for ova should be made. A common infestation is with the *Ascaris lumbricoides*, which in children may be the cause of a low grade fever. The eggs are readily found in the stool.

**Trichinosis.**—Trichinosis, which is endemic and far more prevalent than is generally thought, is also characterized by temperature elevation and is easily mistaken for some other

condition or is overlooked entirely. During the period of migration and encystment, which may take several weeks, there is frequently a low grade fever.

Diagnosis is usually established first from a history of ingestion of raw or poorly cooked pork, although this is not by any means invariably obtained, the patient having forgotten the incident. The symptoms are at times violent at the beginning, with severe gastro-intestinal distress. Later a myositis appears or in mild cases this may be the first complaint.

There are several procedures which help establish a diagnosis. An eosinophilia is the rule, although it may be absent in severe or fatal cases. *Trichinella* larvae may be found in the stool or in centrifuged blood. Biopsy of a small piece of biceps muscle may show the larvae after the encystment stage has been reached. The *Backman intradermal test* is simple and fairly conclusive evidence of trichinosis. It is performed by injecting 0.1 cc. of a 1:5000 dilution of specific antigen into the forearm. A white center with a surrounding erythema 5 cm. in diameter arises immediately and reaches a maximum in ten minutes, thereafter gradually fading out.

#### OBSCURE FEVERS FROM OTHER CAUSES

**Blood Dyscrasias.**—The blood dyscrasias may present a diagnostic problem when they are accompanied by fever. The leukemias and aplastic pernicious anemia, when they reach the stage where a fever occurs, usually present no diagnostic problem, as the blood picture is typical. However, Hodgkin's disease and aleukemic leukemia may be more confusing, particularly the former.

**Hodgkin's Disease.**—This disease, which occurs twice as frequently in males as in females, may develop at any age but is seen most frequently in the third decade. The onset is often insidious and the condition may go undiagnosed for months, particularly if the mediastinal glands are the first involved. Ordinarily a unilateral enlargement of a cervical lymph gland ushers in the disease, although glands elsewhere, in the axilla, inguinal region or abdomen, may first manifest the condition. These glands are painless and firm.

Accompanying the progressive glandular enlargement is fever which may be continuous or alternating (Pel-Ebstein type).

Other symptoms include weakness, loss of weight, pallor and pressure symptoms if the enlarged glands interfere with other organs. Extreme pruritus may be an early and annoying



symptom. A diagnosis is established by removal of an enlarged lymph node for microscopic study. Examination should include an x-ray examination of the chest for enlarged mediastinal glands.

Blood studies are of little avail. A mild eosinophilia which accompanies Hodgkin's disease may serve to confuse it with trichinosis unless a biopsy is done.

**Malignant Tumors.**—Fever may be an early sign of an unrecognized malignancy. *Carcinoma of the stomach and bowel*, when ulcerated and secondarily infected, may produce a low grade fever and leukocytosis without sufficient symptoms to call the patient's attention to the underlying condition. *Bronchogenic carcinoma* is also characterized by low grade fever. A careful history will usually lead to investigation of the proper system.

**Disorders of the Heat-Regulatory Mechanism.**—Interference with the methods by which heat is regulated by the body may result in fever. Haldane<sup>7</sup> showed that sitting still in saturated air at 89° F. will result in an increased temperature, and with increased environmental temperatures up to 98° F. as much as 4° increase within an hour was noted. It has been said that continued exposure to excessive heat results in derangement of the heat-regulating mechanism, consequently, in a continued hot and damp atmosphere, elevation in body temperature, restlessness, headache and tachycardia result. Muscular cramps and nausea and vomiting then supervene. Diagnosis is usually obvious from the history, and treatment consists of removal to a normal environment and establishment of a physiologic salt and water balance.

One should be certain that continued fever is not the result of treatment rather than of the original disease for which treatment was instituted. Reactions to serums and drugs used in therapy are not unusual and fever may be an expression of this reaction.

*Treatment* has been mentioned as each subject has been discussed. It depends entirely on the underlying cause. The facetious remark that "all fevers should be treated for six days with sulfanilamide and if they persist the patient should be examined" shows one reason why a valuable therapeutic agent is so often discredited. The rapid advances in chemotherapy have made our task in handling infections a much simpler one. However to treat fever as such is archaic and useless. The genesis of the fever must be discovered before proper treat-

ment can be instituted, and measures introduced before this is accomplished may cloud the issue and make accurate diagnosis difficult or impossible.

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